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Coloured alkali salts from *sym*-trinitrobenzene derivatives. Part III. Picramide derivatives. By R. C. Farmer

384. *The Mass-law Effect in the Hydrolysis of Dichlorodiphenylmethane.*

By G. Kohnstam and B. Shillaker.

The rate of hydrolysis of dichlorodiphenylmethane is controlled by the rate at which one of the C–Cl linkages undergoes heterolysis. This process involves the unimolecular mechanism, S_N1, and the present study aimed at obtaining further information about the behaviour of the resulting carbonium ion, Ph_2ClC^+, in aqueous acetone. The mass-law constant,[1] which reflects the competition of chloride ions and water for this ion, decreases with increasing ionising power of the solvent, and its temperature coefficient is independent of the solvent composition. This behaviour is consistent with the assumption of Born charging for the solvated species involved, or with differences in the extent of their solvation; alternatively, both these factors may be responsible.

If the S_N1 heterolysis of the C–Cl linkage involves intermediate ion-pairs,[2] our results show that only the fully developed carbonium ion reacts with water and with anions.

In the S_N1 hydrolysis of an organic halide

$$RX \underset{2}{\overset{1}{\rightleftharpoons}} R^+ + X^- \xrightarrow[H_2O]{3} ROH + H^+ + X^-$$

the competition of solvent molecules and " common " anions for the fully developed carbonium ion is of interest. The relevant information is contained in the mass-law constant ($\alpha^0 = k_2^0/k_3^0$, where the superscripts refer to zero ionic strength) which can be evaluated *via* the electrostatic treatment of Hughes, Ingold, and their co-workers.[1] Little is known of the variation of this constant with changing solvent composition and the present paper reports an extension of previous work on the hydrolysis of dichlorodiphenylmethane [3] to two further solvents, " 80% " and " 70% " aqueous acetone.† The rate-determining step in this reaction is the ionisation of one of the C–Cl linkages, and the resulting carbonium ion, Ph_2ClC^+, has a fairly large mass-law constant. The system is therefore well suited for studying the effects of solvent changes on α^0.

Experimental

The experimental methods were similar to those described previously.[3] The thermostat for temperatures below 0° consisted of a well-stirred ethanol–water mixture in a large Dewar vessel. Cooling was effected by filling the inner of two concentric glass tubes with solid carbon dioxide, and the outer with sufficient ethanol to keep the temperature of the bath just below the desired value in the absence of heating. A 5w intermittent heater was controlled by a conventional toluene–mercury regulator, and kept the temperature constant to within $\pm 0{\cdot}01°$.

The hydrolysis of *ca.* 0·005M-dichlorodiphenylmethane was studied at 0° in " 80% " acetone, and at $-9{\cdot}61°$ and $-21{\cdot}50°$ in the " 70% " solvent where the reaction at 0° was too rapid to permit accurate measurements. The reactions were followed by noting the development of acidity, and gave integrated first-order rate coefficients ($\bar{k}$) which always decreased as the hydrolysis proceeded (see Table 2). In the " 70% " solvent, experiments were also carried out at $-9{\cdot}61°$ in the presence of potassium chloride, potassium bromide, and their mixtures at an initial ionic strength of 0·0515. The instantaneous rates at this ionic strength were obtained by extrapolating the integrated first-order rate coefficients to " zero time," and followed the relation

$$10^4k = 3{\cdot}25/(1 + 32{\cdot}9[Cl^-]) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

† Throughout this paper a " x% " solvent refers to a mixture of acetone and water in the ratio $x : 100 - x$ by vol.

[1] Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979.
[2] Winstein *et al.*, *J. Amer. Chem. Soc.*, 1958, **80**, 169, 459; and earlier papers.
[3] Bensley and Kohnstam, *J.*, 1955, 3408.

This is illustrated in Table 1 where the values calculated from this equation are compared with those observed.

TABLE 1. *Instantaneous rates (k, in sec.$^{-1}$) at ionic strength* 0·0515 *in "* 70% *" acetone at* −9·61°.

[KBr] + [KCl] = 0·0500, $[Cl^-]_0$ = [KCl] + 0·0015 ± 0·0005,† 0·0015 ⩽ $[Cl^-]_0$ ⩽ 0·0510.

$10^3[Cl^-]_0$	1·5	14·5	26·4	38·5	51·0
10^4k, obs.	3·12	2·16	1·72	1·47	1·20
10^4k, calc.	3·10	2·20	1·74	1·43	1·21

The subscript 0 refers to "zero time."
† Due to hydrolysis before the initial reading.

The results of any one kinetic run gave the rate of ionisation at zero ionic strength (k_1^0) and the mass-law constant (α^0) from the equation

$$I/t = k_1^0 - \alpha^0 J/t \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)\dagger$$

where

$$I = \int_0^x \frac{\text{antilog}_{10}\, B\sigma(b + c + 2x)}{a - x}\, dx$$

and

$$J = \int_0^x \frac{(c + 2x)\ \text{antilog}_{10}\, A(b + c + 2x)}{a - x}\, dx$$

a = $[Ph_2CCl_2]$ at time $t = 0$, $a - x$ = $[Ph_2CCl_2]$ at time t, b and c are the initial bromide- and chloride-ion concentrations, respectively, $b + c + 2x$ is the ionic strength at time t,‡ $A = -1{\cdot}815 \times 10^6(DT)^{-3/2}$, $B = -0{\cdot}912 \times 10^{16}(DT)^{-2}$, D and T are the dielectric constant and absolute temperature, respectively, and σ is the ionic-strength constant [1] whose value was assumed to be the same ($1{\cdot}1 \times 10^{-8}$) as in the solvents previously examined. Eqn. (2) is readily deduced from the electrostatic treatment by Hughes, Ingold, and their co-workers,[1] and the evaluation of the integrals I and J has already been discussed.[3] Data for a typical run are given in Table 2, and our main results are summarised below (k_1^0 in sec.$^{-1}$, α^0 in mole^{-1} l.):

(i) "80%" acetone at 0°, 4 experiments: $10^4k_1^0 = 1{\cdot}438 \pm 0{\cdot}004$, $\alpha^0 = 98{\cdot}8 \pm 0{\cdot}8$
(ii) "70%" acetone at −9·61°, 10 experiments: $10^4k_1^0 = 2{\cdot}912 \pm 0{\cdot}020$, $\alpha^0 = 62{\cdot}7 \pm 0{\cdot}7$
(iii) "70%" acetone at −21·50°, 4 experiments: $10^5k_1^0 = 5{\cdot}503 \pm 0{\cdot}038$, $\alpha^0 = 57{\cdot}2 \pm 2{\cdot}0$.

TABLE 2. *Reaction of dichlorodiphenylmethane with "* 80% *" aqueous acetone at* 0°. (Run C.)

(5 ml. samples titrated with 0·004988N-NaOH; $A = -1{\cdot}861$; $B\sigma = -1{\cdot}038$.)

t (sec.)	Titre (ml.)	10^4k (sec.$^{-1}$)	$10^4I/t$ (sec.$^{-1}$)	$10^7J/t$ (mole l.$^{-1}$ sec.$^{-1}$)	t (sec.)	Titre (ml.)	10^4k (sec.$^{-1}$)	$10^4I/t$ (sec.$^{-1}$)	$10^7J/t$ (mole l.$^{-1}$ sec.$^{-1}$)
0	0·37	—	—	—	5068	6·77	1·134	1·124	3·295
1461	2·87	1·280	1·276	1·775	5948	7·42	1·104	1·093	3·491
2058	3·69	1·249	1·242	2·133	6878	8·12	1·096	1·083	3·769
2643	4·41	1·222	1·215	2·427	8083	8·85	1·071	1·058	4·001
3263	5·06	1·184	1·176	2·649	∞	15·01	—	—	—
4163	6·00	1·166	1·157	3·037					

$10^4k_1^0 = 1{\cdot}441$ sec.$^{-1}$, $\alpha^0 = 99{\cdot}1$ mole^{-1} l.

DISCUSSION

The data now available for the ionisation of dichlorodiphenylmethane in aqueous acetone at 0° and zero ionic strength are summarised in Table 3. The rate of ionisation (k_1^0) changes almost 100-fold on passing from "70%" to "85%" acetone; Fainberg

† We take this opportunity to correct errors in the earlier paper [3] which were inadvertently missed during proof-reading. Equation (ii) should be identical with the present equation (2), A (Tables 3 and 4) should be negative, and the constants C and D (p. 3416) should be given by

$$C = 10^4k_1^0\ \text{antilog}_{10}(-B\sigma\mu)\ \text{and}\ D = \alpha^0\ \text{antilog}_{10}(A\mu^{\frac{1}{2}} - B\sigma\mu).$$

‡ The hydrolysis of dichlorodiphenylmethane yields benzophenone and, hence, two chloride ions per mole.

and Winstein's data for t-butyl chloride [4] lead to a similar change at this temperature. The activation energy of the ionisation process (E_1^0) is virtually independent of the solvent composition,† in agreement with previous observations on S_N1 reactions.[4, 6, 7] The difference between the activation energies for the reactions of chloride ions and water with the fully developed carbonium ion ($E_2^0 - E_3^0$) also appears to be insensitive to changes in the solvent. The most significant feature of the present results is the decrease in the mass-law constant, α^0, as the solvent is made more aqueous. Before this observation can be discussed in detail, it is necessary to consider whether it arises from some imperfection in the electrostatic treatment [1] adopted.

TABLE 3. *Effect of solvent composition on the rate of ionisation and mass-law constant in the reaction of dichlorodiphenylmethane with aqueous acetone at* 0°.

" % " Acetone	85% †	80%	75% †	70%
$10^4k_1^0$ (sec.$^{-1}$)	0·530	1·438	4·386	14·30 ‡
α^0 (mole^{-1} l.)	126 ± 4·2	98·8 ± 0·8	79·4 ± 0·6	67·2 ± 2·0 ‡
E_1^0 (kcal.)	17·60	—	—	18·40
$E_2^0 - E_3^0$ (kcal.) §	0·9 ± 0·4	—	—	1·0 ± 0·4

† From Bensley and Kohnstam's data.[3] ‡ Calculated from results at lower temperatures. § From the temperature coefficient of ln α^0.

Ionic Activity Coefficients.—Eqn. (2) assumes that ionic activity coefficients are given by Debye's limiting law, an assumption which becomes increasingly less valid as the ionic strength is increased, or the dielectric constant of the solvent reduced. " Limiting-law activity coefficients " are then too low, leading to too small a value for the integral J and, hence, to too large a value for α^0. This could account for the variation of α^0 with changes in the solvent composition. However, experiments in " 70% " and " 75% " acetone gave the same value of α^0 when carried out in the absence of added electrolytes and at ionic strength 0·05, and it does not therefore seem likely that the observed behaviour of α^0 results from the use of " limiting-law activity coefficients."

Ion-pair Formation by Electrolytes.—The present results have been calculated on the assumption that all electrolytes are completely dissociated. It can easily be shown that, if this is not the case, mass-law constants obtained from eqn. (2) are too small, the error increasing as the ion-pair dissociation constant of the electrolyte decreases. The values of α^0 should then decrease as the solvent is made less aqueous, contrary to our observations.

In any case, it is not considered that ion-association is large enough to have a significant effect on the value of α^0 in any of the systems under consideration. In " 75% " acetone, the dissociation of lithium bromide is virtually complete,[8] and this should therefore also apply to potassium bromide which has almost the same dissociation constant as the lithium salt in " 90% " acetone;[9] there is little reason to believe that potassium chloride is appreciably more associated than its bromide.‡ It also seems reasonable to assume that hydrochloric acid behaves in a similar manner to hydrobromic acid; the latter has a dissociation constant of 6×10^{-3} in " 90% " acetone and is completely dissociated in the " 70% " solvent.[9] The dissociation constant to be expected for hydrochloric acid in " 85% " acetone is then such that the neglect of association in the acid produced by the hydrolysis

† The two values of E_1^0 in Table 3 were obtained from data at different temperatures. A negative temperature coefficient is to be expected for E_1^0 since the ionisation of C–Cl involves an increase in the polarity of the reacting system,[5, 6] and it is therefore considered that the two values of E_1^0 will differ by less than 0·5 kcal. at 0°.

‡ Experiments in the presence of salts were only carried out in " 75% " and " 70% " acetone.

[4] Fainberg and Winstein, *J. Amer. Chem. Soc.*, 1957, **79**, 5937.
[5] Robertson, *Canad. J. Chem.*, 1955, **33**, 1536; 1957, **35**, 613; Bensley and Kohnstam, *J.*, 1956, 287; 1957, 4747.
[6] Tommila, Tilikainen, and Voipio, *Ann. Acad. Sci. Fennicae*, 1955, *A*, No. II.
[7] Brown and Hudson, *J.*, 1953, 3352.
[8] Olson and Konecny, *J. Amer. Chem. Soc.*, 1953, **75**, 5801.
[9] Nash and Monk, *J.*, 1955, 1899.

of 0·005M-dichlorodiphenylmethane only affects the value of α^0 within the limits of the experimental error. The resulting error is even smaller in the more aqueous solvents.

Specific Salt Effects.—The electrostatic treatment on which eqn. (2) is based assumes that the acceleration of the ionisation of the C–Cl linkage by added electrolytes, the ionic-strength effect, results from ion-atmosphere stabilisation of the transition state and depends only on the ionic strength of the solution. Earlier criticisms of this assumption [10,11] are often based on observations in systems where ion-pair formation may be significant, but highly specific salt effects have recently been observed by Duynstee and Grunwald for the ionisation of 1-methyl-2-phenylpropyl toluene-*p*-sulphonate in 50% aqueous dioxan.[12] These authors conclude that two additional factors may contribute to the ionic-strength effect: (i) a salt-induced medium effect which arises from the different effects of electrolytes on the activities of the solvent components,[13] similar to an earlier suggestion by Lucas and Hammett,[14] and (ii) short-range interactions, such as complex formation with the substrate.

Specific salt reactions do not, however, appear to be operating in the present reactions. First, the constant C in eqn. (5) (cf. eqn. 1) represents the initial rate of ionisation in 0·05M-potassium chloride and in 0·05M-potassium bromide. Secondly, the rate of ionisation at zero ionic strength, k_1^0, which was obtained from experiments on 0·005M-solutions containing no added salts, leads to a value for the rate at ionic strength 0·05 [k_1^0 antilog$_{10}$ ($-B\sigma\mu$) = $3{\cdot}15 \times 10^{-4}$, where μ is the ionic strength] which agrees with the observed value ($C = 3{\cdot}25 \times 10^{-4}$) as well as can be expected for initial rates. The two additional effects proposed by Duynstee and Grunwald are therefore either negligibly small or of the same magnitude for hydrochloric acid, potassium chloride, and potassium bromide in the present systems, and thus have no significant influence on our values for the mass-law constant.

The Variation of the Mass-law Constant with Solvent Composition.—The observed decrease of the mass-law constant with increasing water content of the solvent confirms and extends previous findings.[3] A qualitative explanation of this result has already been given, and a more quantitative interpretation can now be attempted.

From the definition of the mass-law constant we have

$$\boldsymbol{RT} \ln \alpha^0 = \boldsymbol{RT} \ln (k_2^0/k_3^0) = \Delta G_3^* - \Delta G_2^*$$

where ΔG_2^* and ΔG_3^* are the free energies of activation for the reaction between the carbonium ion and chloride ions, and for the hydrolysis of the carbonium ion, respectively. Solvation of charged species is an essential feature of reaction by mechanism S_N1, and it seems reasonable to assume that the two processes now under consideration may involve changes in solvation by water, but not changes in solvation by acetone. The difference between the two free energies of activation then becomes the difference between the standard free-energy changes of the two processes:

$$R^+ \text{ (solv.)} + Cl^- \text{ (solv.)} \longrightarrow R^{z+}\cdots Cl^{z-} \text{ (solv.)} + n_2H_2O$$

$$R^+ \text{ (solv.)} \longrightarrow R\text{–}\overset{+}{O}H_2 \text{ (solv.)} + n_3H_2O$$

where the parameter z represents the degree of charge development in the transition state of the ionic recombination and has a value between zero and unity; n_2 is most unlikely to be negative and is probably positive since a reduction of charge can be expected to lead to decreased solvation, and n_3 may well be zero.[1] Hence,

$$\boldsymbol{RT} \ln \alpha^0 = \bar{G}_a^* + \bar{G}_b^* - \bar{G}_c^* - (n_2 - n_3)\bar{G}(H_2O) \quad . \quad . \quad . \quad . \quad (3)$$

[10] Spieth and Olson, *J. Amer. Chem. Soc.*, 1955, **77**, 1412.
[11] Fainberg and Winstein, *ibid.*, 1956, **78**, 2763.
[12] Duynstee, Thesis, Amsterdam, 1959.
[13] Baughman, Grunwald, and Kohnstam, *ibid.*, in preparation.
[14] Hammett and Lucas, *ibid.*, 1942, **64**, 1928.

where the $\bar{G}^*$ terms represent standard chemical potentials, $\bar{G}(H_2O)$ is the chemical potential of water in the solvent, and the subscripts a, b, c refer to Cl^- (solv.), $R\overset{+}{-}OH_2$ (solv.) and $R^{z+}—Cl^{z-}$ (solv.), respectively.

The two transition-state structures being assumed to be constant over the range of solvents under consideration, the effect of solvent changes on the chemical potentials will be given by the Born equation [15] for the fully developed ions, and by the Kirkwood equation [16] for the dipolar structure.† Equation (3) then takes the form

$$\boldsymbol{RT} \ln \alpha^0 = \text{constant} + (\boldsymbol{Ne}^2/2\varepsilon)[1/r_a + 1/r_b - 3(z\boldsymbol{d})^2/2r_c^3] - (n_2 - n_3)\boldsymbol{RT} \ln a \quad (4)\ ‡$$

where ε is the dielectric constant, a the activity of water in the solvent, $z\boldsymbol{e}\boldsymbol{d}$ the dipole moment of $R^{z+}---Cl^{z-}$ (solv.), and the r's the radii of the solvated species.

In the present solvents $1/\varepsilon$ is virtually a linear function of ln a, and the " best " straight line obtained by plotting ln α^0 against $1/\varepsilon$, or against ln a, predicts the observed values of α^0 within the limits of experimental error. If the transition state for the ionic recombination reaction carries fully developed charges (*i.e.*, $z = 1$),[18] the square bracket in eqn. (4) could be zero, whence $n_2 - n_3 = 4{\cdot}2$; this value is not impossibly large.§ Alternatively, if $n_2 - n_3 = 0$, the assumption that $d = r_c$ and reasonable values for the radii ($r_a = 4{\cdot}6$ Å,[17] $r_b = r_c = 7$ Å) lead to $z = 0{\cdot}63$, consistent with the usual view that this type of transition state carries approximately half-developed charges.[1] Our results are thus fully consistent with the considerations on which equation (4) is based, but it is unfortunately not possible to establish whether the variation of α^0 with solvent composition arises solely from the " electrostatic " effect (the term in $1/\varepsilon$), or whether differential solvation effects also contribute.

The constancy of $E_2^0 - E_3^0$ within the limits of experimental error (see Table 3) does not alter this conclusion. From eqn. (4) we have

$$E_2^0 - E_3^0 = \boldsymbol{RT}^2 \mathrm{d} \ln \alpha^0/\mathrm{d}T = \text{constant} - (\boldsymbol{Ne}^2/2\varepsilon)[1/r_a + 1/r_b - 3(z\boldsymbol{d})^2/2r_c^3](1 + T\,\mathrm{d} \ln \varepsilon/\mathrm{d}T) + (n_2 - n_3)\bar{L}$$

where $\bar{L}$ is the relative partial molar enthalpy of water in the solvent, and can be obtained from available data.[20] This equation predicts that a change from " 85% " to " 70% "

† It has often been found that the Born equation does not apply to unsolvated ions, but it is generally taken to be valid for solvated ions.[17] It seems reasonable to assume that this also applies to the Kirkwood equation.

‡ The last term in the square bracket of equation (4), the Kirkwood term, arises as follows. The Kirkwood equation for the free-energy change on transferring a dipole of moment $z\boldsymbol{e}\boldsymbol{d}$ and radius r from vacuum to a medium of dielectric constant is

$$\Delta G_D = -\frac{\varepsilon - 1}{2\varepsilon + 1} \cdot \frac{(z\boldsymbol{e}\boldsymbol{d})^2}{r^3} = \text{constant} + \frac{3}{2(2\varepsilon + 1)} \cdot \frac{(z\boldsymbol{e}\boldsymbol{d})^2}{r^3}$$
$$= \text{constant} + 3(z\boldsymbol{e}\boldsymbol{d})^2/4\varepsilon r^3$$

with negligible error for the dielectric constants now under consideration.

§ This value probably represents an overestimate, even for an upper limit, since it is likely that changes in the dielectric constant have a larger effect on the stabilities of two separate ions than on the stability of a dipole carrying fully developed charges. For $r_a = 4{\cdot}6$ Å, $r_b = r_c = d = 7$ Å, and $z = 1$, equation (4) yields $n_2 - n_3 = 2{\cdot}0$. Water activities were obtained from Ewert's data at 25°,[19] ideal behaviour of the vapours over aqueous acetone being assumed, and from Kister and Waldmann's thermal data; [20] dielectric constants are from Akerlof's data.[21]

[15] Born, *Z. Phys.*, 1920, **1**, 45.
[16] Kirkwood, *J. Chem. Phys.*, 1934, **2**, 351.
[17] Eley and Evans, *Trans. Faraday Soc.*, 1938, **34**, 1093; Coulson and Everett, *ibid.*, 1940, **36**, 633; Oiwa, *J. Phys. Chem.*, 1957, **61**, 1587; Buckingham, *Discuss. Faraday Soc.*, 1958, **24**, 151.
[18] Baughan, Evans, and Polanyi, *Trans. Faraday Soc.*, 1941, **37**, 377; Evans, *ibid.*, 1946, **42**, 719; Franklin, *ibid.*, 1952, **48**, 443.
[19] Ewert, Thesis, Brussels, 1935.
[20] Kister and Waldmann, *J. Phys. Chem.*, 1958, **62**, 245.
[21] Akerlof, *J. Amer. Chem. Soc.*, 1932, **54**, 4125.

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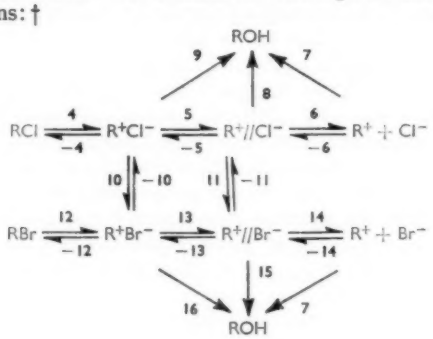
acetone alters $E_2^0 - E_3^0$ by less than 0·2 kcal. for all values of $n_2 - n_3$ between zero and 4·2; the standard error of the observed $E_2^0 - E_3^0$ is 0·4 kcal./mole.

Ion-pair Intermediates.—The present discussion has been based on Hughes and Ingold's scheme for the S_N1 reactions of the C–Cl linkage:

$$RCl \underset{2}{\overset{1}{\rightleftharpoons}} R^+ + Cl^- \xrightarrow[H_2O]{3} ROH + H^+ + Cl^-,\ R^+ + Br^- \rightleftharpoons RBr \quad . \quad . \quad . \quad . \quad . \quad (i)$$

Here only the fully developed carbonium ion reacts with water and with anions.

Results observed in the acetolysis of sulphonic esters led Winstein and his co-workers to conclude that ionisation proceeds *via* intermediate ion-pairs which are capable of reacting directly with water and anions.[2] This scheme can be represented as follows when applied to the present reactions: †



. . . . . (ii)

where R^+X^- represents the "internal" ion-pair and $R^+//X^-$ the "external" or "solvent-separated" ion-pair. If the present reactions follow this scheme, the conclusions reached in the preceding section could be seriously in error.

Any reaction scheme must, however, be consistent with the instantaneous hydrolysis rate observed in "70%" acetone and ionic strength 0·051 over chloride-ion concentrations ranging from 0·0015M to 0·051M: *viz.*,

$$k = C/(1 + \alpha[Cl^-]) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where C and α are constants (see Table 1). The rate coefficients of the individual reaction stages should be independent of chloride- and bromide-ion concentrations at constant ionic strength, and the application of the stationary state principle to the ion-pairs, the carbonium ion, and the organic bromide shows that scheme (ii) only leads to eqn. (5) if

$$C = \frac{k_4}{1 + k_{-45}k_5 + k_{-4}k_{-5}/k_5k_6}, \qquad \alpha = \frac{k_{-4}k_{-5}k_{-6}/k_5k_6k_7}{1 + k_{-4}k_5 + k_{-4}k_{-5}/k_5k_6} \quad . \quad . \quad (6)$$

This result is identical with that obtained for the scheme

$$\left.\begin{array}{l} RCl \underset{-4}{\overset{4}{\rightleftharpoons}} R^+Cl^- \underset{-5}{\overset{5}{\rightleftharpoons}} R^+//Cl^- \underset{-6}{\overset{6}{\rightleftharpoons}} R^+ + Cl^- \xrightarrow{7} ROH + H^+ + Cl^- \\ R^+ + Br^- \rightleftharpoons R^+//Br^- \rightleftharpoons R^+Br^- \rightleftharpoons RBr \end{array}\right\} \quad . \quad . \quad (iii)$$

and requires that only the fully developed carbonium ion reacts with water and anions. ‡

It is now necessary to express the mass-law constant, α^0, in terms of the rate coefficients of the individual reaction stages involved in solvolysis by scheme (iii). Mass-law constants

† It is usually considered that the internal ion-pair, R^+X^-, does not react with anions,[2] but this process has now been included to allow for all possibilities.

‡ A similar conclusion has already been reached for a simplified version of scheme (ii) on the basis of experiments in "75%" acetone over the range 0·025—0·050M for the chloride-ion concentration.[2]

were obtained from eqn. (2) which is based on Hughes and Ingold's simpler scheme, (i), and on the electrostatic treatment proposed by these workers;[1] this approach is also consistent with eqn. (5) and requires that $\alpha = k_2/k_3 = \alpha^0 \text{ antilog}_{10} (A\mu^{\frac{1}{2}} - B\sigma\mu)$. Experiments at different ionic strengths gave the same value of α^0, within the limits of experimental error, and this value yields $\alpha = 33{\cdot}7$ in " 70% " acetone at $-9{\cdot}61°$ and ionic strength 0·051, in good agreement with the observed value of 32·9 [see eqn. (1)]. It can therefore be concluded that reaction by scheme (iii) requires the same variation of α with changing ionic strength as scheme (i) and, hence, that α^0 represents the value of α at zero ionic strength whichever of the two schemes is operating.

Qualitatively, the observed behaviour of the mass-law constant with changing solvent composition is fully consistent with reaction by scheme (iii). Rate coefficients for processes involving the approach of opposite charges will increase less with increasing ionising power of the solvent than rate coefficients for their separation (or for the spreading of an existing charge); eqn. (6) shows that α, and hence α^0, should therefore decrease with increasing water content of the solvent, as observed. The more quantitative interpretation discussed in the preceding section also holds true for reaction by scheme (iii) provided that

$$k_{-4}/k_5 + k_{-4}k_{-5}/k_5k_6 \ll 1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

we then have $\alpha^0 = k^0_{-4}k^0_{-5}k^0_{-6}/k^0_5k^0_6k^0_7$, whence it can easily be shown that $RT \ln \alpha^0$ is still given by eqn. (3); the only difference is that $R^{\delta+}\cdots Cl^{\delta-}$ (solv.) now represents the transition state in step -4 and is not formed directly from the fully developed ions.

There is some evidence that inequality (7) is valid, at least as a first approximation,* but this evidence is not conclusive, and the denominator in equation (6) could be greater than unity; this would complicate any attempt to interpret the behaviour of α^0 quantitatively. It must, however, be stressed that the available evidence does not allow us to distinguish between schemes (i) and (iii) for the hydrolysis of dichlorodiphenylmethane. Since ion-pair intermediates have often been found to undergo direct solvolysis, the absence of any such reactions now (cf. p. 1920) may well arise from the fact that no ion-pairs are involved as intermediates in the present systems. This would mean hydrolysis by scheme (i), as originally envisaged by Hughes and Ingold.

We thank Professor E. Grunwald for valuable discussions and for making unpublished results available to us, and the Ministry of Education for the award of a State Scholarship (to B. S.).

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* If inequality (7) is valid, application of the Brönsted equation to the rate coefficients shows that schemes (i) and (iii) require the same variation of α^0 with changing ionic strength, as observed. Inequality (7) also demands that the rate of step 4 (k_4[RCl]) should be the same as the rate of hydrolysis in the absence of " common " ions (C[RCl]). For 1-methyl-2-phenylpropyl toluene-*p*-sulphonate in 50% aqueous dioxan step 4 occurs about 60% more rapidly than hydrolysis,[12] but Winstein's results [3] suggest that this discrepancy should be less for a substrate with a greater facility for ionisation and it may well vanish for dichlorodiphenylmethane. The identity of titrimetric and polarimetric rates in the reaction of 1-phenylethyl chloride with aqueous ethanol [22] is consistent with this view.

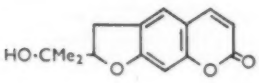
[22] Ward, *J.*, 1927, 445.

385. *The Isolation and Constitution of Marmin, a New Coumarin from* Aegle marmelos, *Correa.*

By A. Chatterjee and A. Bhattacharya.

Umbelliferone, skimmianine, a new coumarin (marmin), and γ-sitosterol have been isolated from the immature bark of *Aegle marmelos* Correa. The constitution of marmin has been established as 7-(3 : 7-dihydroxy-3 : 7-dimethyloctyloxy)coumarin.

Aegle marmelos (Fam. *Rutaceae*), commonly known as bael, is a large or medium-sized tree of wide occurrence in India. It is reputed to give a valuable drug and produces besides essential oil various coumarins and alkaloids in its various parts.[1-3] The constituents vary considerably with the maturity of the specimens. The mature trunk-bark produces umbelliferone, γ-fagarine[1] (4 : 8-dimethoxyfuroquinoline), and marmesin[1] (I) whereas the



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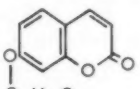

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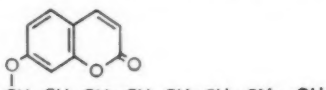

(III)

contents of an immature species are a new coumarin, marmin, $C_{19}H_{26}O_5$, m. p. 124°, umbelliferone and a different alkaloid, skimmianine (4 : 7 : 8-trimethoxyfuroquinoline). With the maturity of the bark the yields of marmin and skimmianine decrease, the contents of marmesin, γ-fagarine, and essential oil increasing. In highly mature bark there is no marmin or skimmianine.

The isolation and constitution of marmin are described in the present communication.

Hydrochloric acid washings of ethereal trunk-bark extracts of *A. marmelos* yielded a basic portion from which skimmianine (yield, 0·003%) was isolated. Chromatography of the residue obtained from the non-basic ether extract yielded γ-sitosterol (0·015%), marmesin (0·012%), and marmin (0·07%); umbelliferone (0·02%), retained in the column, could only be taken out with boiling ethanol. Marmin has $[\alpha]_D^{30}$ +25, pK_a 10·11, and an ultraviolet absorption spectrum similar to that of umbelliferone methyl ether; this and the infrared spectrum disclose a δ-hexenolactone grouping. Marmin does not consume perphthalic acid, is indifferent towards ferric ion, gives a negative Angeli–Rimini test, is free from methoxy, methylenedioxy, ketone, and aldehyde functions, and is shown to contain a coumarin nucleus by its behaviour towards alkali. Since it fails to produce an α-glycol with oxalic acid and does not react with diethylamine and potassium chloride, the presence of an epoxide group is excluded. It contains two active hydrogen atoms, which in absence of a methylene group, appear to be associated with hydroxyl groups. The latter were indifferent towards phthalic anhydride, 3 : 5-dinitrobenzoyl chloride, and toluene-*p*-sulphonyl chloride, from which the hydroxyl functions in marmin appeared to be tertiary (cf. below). Treatment with acetic acid, phosphorus oxychloride, phosphoric oxide (in benzene), aqueous oxalic acid, or acetic anhydride at their b. p.s. resulted in a cleavage to umbelliferone together with an oil (terpene), which was extremely sensitive to heat and acids and could not be characterised. Umbelliferone was also obtained from marmin during its thermal decomposition and catalytic hydrogenation, which recalled the

[1] Dutta, Proc. Acad. Sci., United Province, Agra, Oudh, India, 1935, **56**; Späth, Bose, Grüber, and Guha, *Ber.*, 1937, **70**, 1021; Chatterjee and Saha, *J. Indian Chem. Soc.*, 1957, **34**, 228; Chatterjee and Bose, *ibid.*, 1952, **29**, 425; Chakravarti and Das Gupta, *J.*, 1958, 1580; Chatterjee and Srimany, XVIth Congr. Internat. Pure Appl. Chem., Paris, 1957, Part II, p. 199; Chatterjee, Bose, and Srimany, *J. Org. Chem.*, in the press; Chatterjee and Roy, Proc. 44th Indian Sci. Congr., 1957, Part III, p. 124; Chatterjee and Mitra, *J. Amer. Chem. Soc.*, 1949, **71**, 606; Chaudhury, Ghosh, and Chatterjee, Proc. 46th Indian Sci. Congr., 1959, Part III, p. 142.

[2] Mookerjee, *Current Sci.*, 1943, **12**, 209.

[3] Chakravarty, *J. Indian Chem. Soc.*, 1944, **21**, 401.

behaviour of geranyloxy- and farnesyloxy-coumarins.[4] Marmin suffered spontaneous hydrolysis with glacial acetic acid, like coumarins containing isoprenoid ether groups,[5] to umbelliferone and a terpenaceous oil, from which it followed that marmin was an umbelliferone ether (II).

Treatment of marmin with periodic acid or lead tetra-acetate, even at elevated temperature, failed to produce an aldehyde or ketone, which established that none of the two tertiary hydroxyl groups and the potential hydroxyl group of the ether (II) were vicinal. However, treatment with chromic acid afforded umbelliferone, acetone, and lævulic acid. This, together with the presence of two tertiary hydroxyl groups and expectation of a head-to-tail terpene structure, indicates that marmin has structure (III).

Experimental

M. p.s were determined with a Kofler block. Ultraviolet spectra refer to alcohol solutions in a Beckman spectrophotometer Model DU. The microanalyses were carried out by Mr. W. Manser, Zürich, Switzerland, and Mrs. C. Dutta, University College of Science and Technology, Calcutta. During chromatography the eluants were collected in fractions of 15 c.c. each unless otherwise stated.

Extraction.—Milled trunk-bark (4 kg.) of *Aegle marmelos* Correa was extracted (Soxhlet) with ether (5 l.) for 96 hr. The extracts were concentrated to 200 ml. The concentrate which gave positive Mayer's and Dragendorff's tests for alkaloids was washed with 4N-hydrochloric acid (4 × 50 ml.) until the washings gave negative alkaloid tests.

The hydrochloric acid extract, upon basification with sodium carbonate, liberated skimmianine (0·12 g.) which crystallised from ethyl acetate and acetone in prisms, m. p. and mixed m. p. 175—176° (Found: C, 65·0; H, 5·1; N, 5·30; OMe, 36·1. Calc. for $C_{14}H_{13}O_4N$: C, 64·9; H, 5·0; N, 5·4; OMe, 35·9%).

The ether extract from which alkaloids had been removed was evaporated. The dark residue was chromatographed in benzene (50 ml.) on alumina (1·7 × 40 cm.; 500 g.). In the fractions 11—15 (benzene) appeared crude γ-sitosterol (0·59 g.), m. p. 140—145°. Fractions 16—22 yielded crude marmesin (0·4 g.), m. p. 183—186°. Eluates 23—32 with benzene–ethyl acetate (1 : 1) gave crude marmin (2·8 g.), m. p. 121—123°; umbelliferone (0·8 g.) was finally extracted with boiling ethanol.

γ-Sitosterol was purified by chromatography again over alumina with 1 : 1 benzene–light petroleum (b. p. 40—60°) as eluant. From absolute methanol it formed plates, m. p. and mixed m. p. 146—147° $[\alpha]_D^{25}$ −41·7° (in chloroform) (Found: C, 84·1; H, 12·0. Calc. for $C_{29}H_{50}O$: C, 84·05; H, 12·1%).

Marmesin was obtained pure by several crystallisations from alcohol from which it separated in rods, m. p. and mixed m. p. 190° (Found: C, 68·4; H, 5·7. Calc. for $C_{14}H_{14}O_4$: C, 68·3; H, 5·7%), $\lambda_{max.}$ in ethanol 226, 248, 260, and 335 mμ (log ε 3·98, 3·58, 3·47, 4·16).

Recrystallisation from ethyl acetate–methanol and sublimation at 160°/0·01 mm. afforded pure umbelliferone (0·7 g.), m. p. 232° (Found: C, 66·7; H, 3·6. Calc. for $C_9H_6O_3$: C, 66·7; H, 3·7%), $\lambda_{max.}$ in methanol 216, 327 mμ (log ε 4·09, 4·16).

Chromatography again of crude marmin (2·5 g.) on alumina (100 g.) as above gave, in the fractions eluted with benzene, 0·2 g. of oil; the eluates (200 ml.) with 1 : 1 benzene–ethyl acetate (1 : 1) afforded, after several crystallisations from ethyl acetate, pure *marmin*, m. p. 124° (Found: C, 68·6; H, 7·5; active H, 0·76; *C*-Me, 4·6%; *M*, 325. $C_{19}H_{26}O_5$ requires C, 68·3; H, 7·8; *C*-Me, 4·5%; *M*, 334). In ethanol it showed intense absorption at 213 (no maximum) and 324 mμ (log ε 4·23). Marmin has infrared absorption bands in Nujol at 2·84 (OH), 5·81 (lactone), 6·2 (Ph), 7·18 (side-chain Me), 8·8 and 10·0 μ (phenol ether).

Thermal Decomposition of Marmin.—When marmin (0·5 g.) was heated, a sublimate was obtained at 190°/0·01 mm. It crystallised from ethyl acetate in needles, m. p. 232° alone or mixed with umbelliferone (Found: C, 66·7; H, 3·6. Calc. for $C_9H_6O_3$: C, 66·7; H, 3·7%).

Catalytic Hydrogenation of Marmin.—Marmin (0·3 g.) in ethanol (15 ml.), in presence of Adams platinum oxide (0·05 g.), took up 1 mol. of hydrogen. The solution was diluted with water (50 ml.) and extracted with ether. The extract was washed with 5% aqueous sodium

[4] Dean, "Progress in the Chemistry of Natural Products," ed. Zechmeister, Julius Springer, Vienna, 1952, Vol. IX, p. 225.

[5] Späth and Holzen, *Ber.*, 1933, **66**, 1137; 1935, **68**, 1123.

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hydroxide (3 × 25 ml.). The alkaline extract upon acidification produced dihydroumbelliferone, m. p. and mixed m. p. 133° (Found: C, 65·7; H, 4·9. Calc for $C_9H_8O_3$: C, 65·85; H, 4·85%). The ether residue, when washed with water and dried (Na_2SO_4), gave a terpenaceous oil.

The above experiment was repeated in glacial acetic acid solution with the same results.

Action of Acetic Anhydride on Marmin.—Marmin (0·25 g.) was treated with acetic anhydride–pyridine, kept at 0° for 48 hr., then poured into ice-cold water. A benzene solution of the resinous product was chromatographed over acid-washed alumina. Elution with the same solvent gave a terpenaceous oil. Subsequent washings with ethanol yielded umbelliferone.

Dehydration of Marmin.—Marmin (0·10 g.) in dry benzene (5 ml.) was refluxed with phosphorus oxychloride or phosphoric oxide (0·5 g.) for 2 hr. The benzene solution was decanted and concentrated; umbelliferone, m. p. 232°, separated. The mother-liquor on evaporation gave an oil having a terpene-like odour.

Acid-hydrolysis of Marmin.—(*a*) Marmin (0·5 g.), in glacial acetic acid (2 ml.), was treated with 2 drops of concentrated sulphuric acid, refluxed for 1 hr., then poured into ice-cold water, made alkaline, and extracted with ether. The alkaline mother-liquor (A) was worked up for umbelliferone. The ethereal solution was freed from solvent, and the residue warmed for 5 hr. with 20% sulphuric acid (20 ml.). The hydrolysate was extracted with ether which was washed with 10% alkali solution, then water, and dried. The ethereal solution, on evaporation, left some oil with an odour of geraniol. The alkaline washings were slightly fluorescent but on acidification and extraction with ether did not yield any product.

(*b*) Marmin (0·5 g.) was refluxed in glacial acetic acid (2 ml.) for 2 hr. The product was made alkaline and extracted with ether. The aqueous alkaline solution (B) was worked up for umbelliferone. The ether extract was washed with water, dried, and evaporated, giving an oil with a fragrant odour. This was refluxed with 0·5% methanolic potassium hydroxide for 1 hr. The cold solution was diluted with water and shaken with ether (3 × 50 ml.). These ethereal extracts, on concentration, left an oil with a geraniol-like smell. An attempt to prepare the allophanate was not successful.

The alkaline solutions A and B had a strong blue fluorescence. They were cooled and acidified with hydrochloric acid. A precipitate appeared which was taken up in ether. The ether solution was washed and dried. Evaporation gave umbelliferone (0·4 g.), which crystallised from ethyl acetate in needles, m. p. and mixed m. p. 232° (Found: C, 66·8; H, 3·9%).

Chromic Acid Oxidation of Marmin.—An acetic acid solution (50 ml.) of marmin (4·0 g.) was treated with chromic acid (4·0 g.) in 50% acetic acid (50 ml.) and kept at room temperature for 3 days. The solution was cooled, neutralised with 50% potassium hydroxide solution, and steam-distilled. The distillate was collected in a 5% acetic acid solution of *p*-nitrophenylhydrazine (50 ml.), giving acetone *p*-nitrophenylhydrazone, reddish-yellow needles (from methanol), m. p. and mixed m. p. 148° (0·8 g.) (Found: C, 56·0; H, 5·8; N, 21·6. Calc. for $C_9H_{11}O_2N_3$: C, 55·9; H, 5·9; N, 21·65%).

In a similar experiment acetone was collected over 10% sodium hydroxide solution containing freshly distilled benzaldehyde (4—5 drops). The solution was kept at 0° overnight, then extracted with ether, washed, and dried. The ethereal extract, on concentration, gave dibenzylideneacetone, yellow needles (from methanol), m. p. 110—111° (Found: C, 87·0; H, 6·0. Calc. for $C_{17}H_{14}O$: C, 87·2; H, 6·0%).

The alkaline solution left after the removal of acetone was cooled and acidified (Congo Red) with 4N-sulphuric acid, then saturated with salt and extracted with ether (6 × 50 ml.) which was washed with water, dried, and freed from the solvent. The residual liquid was distilled in a vacuum. The fraction of b. p. 138°/40 mm. yielded lævulic acid. This was purified by chromatography in 1 : 1 benzene–light petroleum (b. p. 40—60°) over " Celite " (1·7 × 30 cm.), with elution by the same solvent mixture. Fractions 5—8 (50 ml. each) gave lævulic acid. An aqueous solution with a saturated 2N-sulphuric acid solution of 2 : 4-dinitrophenylhydrazine produced the yellow dinitrophenylhydrazone, m. p. and mixed m. p. 205—206° (from alcohol) (Found: C, 44·6; H, 4·1; N, 19·0. Calc. for $C_{11}H_{12}O_6N_4$: C, 44·6; H, 4·05; N, 18·9%).

From the residue left after the distillation of lævulic acid umbelliferone was isolated on sublimation at 90°/0·01 mm.

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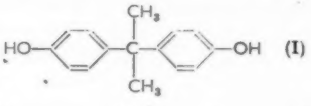
386. *The Mechanism of Epoxide Reactions. Part I. The Reactions of 1 : 2-Epoxyethylbenzene, 1 : 2-Epoxy-3-phenylpropane, and 1 : 2-Epoxy-3-phenoxypropane with Some Secondary Amines.*

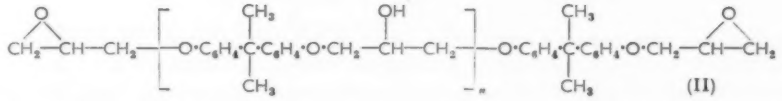
By N. B. Chapman, N. S. Isaacs, and R. E. Parker.

Arrhenius parameters have been determined for the reactions of 1 : 2-epoxyethylbenzene, 1 : 2-epoxy-3-phenylpropane, and 1 : 2-epoxy-3-phenoxypropane with some secondary amines in 99·8% ethanol. In selected cases product analyses have been carried out by infrared spectroscopy whence it is inferred that all the reactions studied give entirely, or almost entirely, "normal" products. The kinetic results therefore refer unambiguously to attack at one position of the epoxide ring. The mechanism of the reactions is discussed and the effect of substituents is analysed in terms of the Taft linear free-energy relation.

Epoxide resins are manufactured by the reaction of an epoxide, usually epichlorohydrin, with a dihydric phenol.[1] From the phenol (I), the resin would have an idealised structure (II). The resin is then cured (*i.e.*, cross-linked), usually by heating it with an amine. The curing process is known to involve reaction between amine molecules and the terminal epoxide groups in the resin. Primary, secondary, and tertiary amines are all used for curing, and especially polyamines (*e.g.*, 2 : 2′-diaminodiethylamine). The present paper



(I)



(II)

records a kinetic study of the reactions between simple epoxides related to the resin (II) and a series of amines. Of the epoxides chosen for study, 1 : 2-epoxy-3-phenoxypropane is clearly related closely to (II), while 1 : 2-epoxyethylbenzene and 1 : 2-epoxy-3-phenylpropane were included in order to determine the effect of structural variation in the epoxide molecule on the rate of the reaction. The amines piperidine, morpholine, and 2-, 3-, and 4-methylpiperidine were chosen in order to determine both the polar and the steric effects of substituents in the amine molecule on the rate. Diethanolamine was included because of its relation to morpholine and to 2 : 2′-diaminodiethylamine. Work is also being carried out with primary amines and this will be reported in a subsequent publication. Ethanol (99·8% w/w) was used as solvent because, in our experience, it is very suitable for the study of nucleophilic substitution, and, in particular, ion exchange with the solvent is usually unimportant.[2]

Previous kinetic work on the reactions of epoxides with amines [3] and with other nucleophiles [4] has usually been restricted to purely aliphatic epoxides. Very few kinetic measurements have been made, and no Arrhenius parameters determined, for the reactions

[1] Narracott, *Brit. Plastics*, 1953, **24**, 120.

[2] Cavell and Chapman, *J.*, 1953, 3392; *Chem. and Ind.*, 1953, 1226.

[3] Smith, Mattsson, and Andersson, *Kgl. Fysiograf. Sallskap. Lund*, 1946, **42**, No. 7, p. 1; Hansson, *Svensk kem. Tidskr.*, 1948, **60**, 183; 1950, **62**, 185; 1954, **66**, 351; 1955, **67**, 246; Andersson, Thesis, Lund, 1955; Eastham *et al.*, *Canad. J. Chem.*, 1951, **29**, 575, 585; *J.*, 1952, 1936; Berbé, *Chimie et Industrie*, 1950, **63**, 3 bis, 492.

[4] Brönsted, Kilpatrick, and Kilpatrick, *J. Amer. Chem. Soc.*, 1929, **51**, 428; Lichtenstein and Twigg, *Trans. Faraday Soc.*, 1948, **44**, 905; Smith, Wode, and Widhe, *Z. phys. Chem.*, 1927, *A*, **130**, 154; Eastham and Latremouille, *Canad. J. Chem.*, 1952, **30**, 169; Nichols and Ingram, *J. Amer. Chem. Soc.*, 1955, **77**, 6547; Petty and Nichols, *ibid.*, 1954, **76**, 4385.

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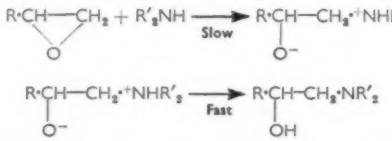
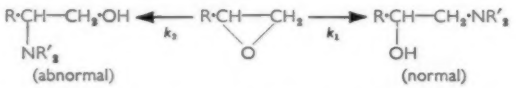
of epoxides containing aryl residues. The reactions of epoxides with nucleophiles have usually been followed either by physical methods (*e.g.*, dilatometry or polarimetry) [5] or by adding a known excess of a reagent for epoxide (*e.g.*, hydrogen chloride or sodium thiosulphate) and determining the excess of this reagent. We have found none of these methods to be entirely satisfactory and we have developed a method for determining the *tertiary* amine produced, namely, by potentiometric titration with perchloric acid in a non-aqueous medium after acetylation of all the secondary amine (see Experimental section). This appears to be the first time these reactions have been followed by direct determination of the product.

The mechanism of epoxide–amine reactions has been shown by previous work often to be a simple S_N2 displacement of oxygen by amine, followed by a rapid proton-transfer (no doubt *via* the hydroxylic solvent):



This simple kinetic picture is, however, complicated by two factors. First, the amine may attack either of the two epoxide-ring carbon atoms to give an amino secondary alcohol or an amino primary alcohol. These two routes are usually referred to as " normal " and " abnormal " ring-opening, respectively:



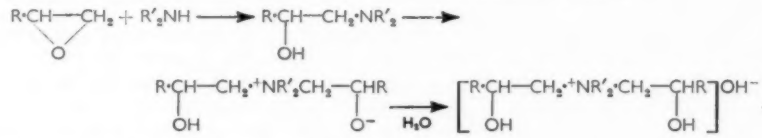
Most of the reactions between epoxides and nucleophiles under basic or neutral conditions give entirely or predominantly the normal isomer. However, there are many cases where no product analysis has been carried out and, even where this has been done, the methods used often leave much to be desired. It is, therefore, not surprising that the position is confused and that there are conflicting reports in the literature.[6] If both reactions occur, the observed second-order rate constant will be the sum of the individual rate constants k_1 and k_2, and the ratio of k_1 to k_2 will be determined by the product ratio. We have investigated the product ratio in three cases (piperidine with each of the three epoxides) by comparing the infrared spectrum of the product with that of each pure isomer. For this purpose the products obtained at 60° (the highest temperature used in the kinetic work) were chosen since it is likely that formation of the abnormal products will be more significant at higher temperatures. (The energy of activation will probably be higher for the formation of the abnormal isomers because of increased steric compression in the transition state.) With 1 : 2-epoxyethylbenzene each product was synthesised by an unambiguous route. With the other two epoxides the abnormal product was synthesised unambiguously, and the normal product by the reaction of the epoxide with piperidine, followed by crystallisation to constant melting point. In the cases of 1 : 2-epoxy-3-phenylpropane and 1 : 2-epoxy-3-phenoxypropane the spectrum of the product was identical with that of the normal isomer. In the case of 1 : 2-epoxyethylbenzene it is just possible to discern the " abnormal " peaks at 945 and 1022 cm.$^{-1}$ in the spectrum of the product; we estimate that these correspond to about 4% of abnormal isomer; since this is such a small amount and is likely to be even less at lower temperatures we have ignored it in kinetic calculations.

As the proportion of abnormal isomer will almost certainly decrease as the steric

[5] Andersson *et al.*, ref. 3.
[6] Swern, Billen, and Knight, *J. Amer. Chem. Soc.*, 1949, **71**, 1152; Hayes, *ibid.*, 1950, **72**, 3321.

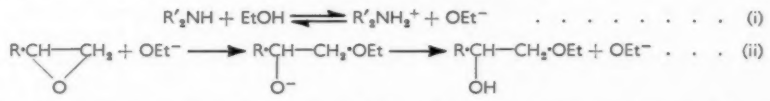
requirements of the reagent increase, and as our other reagents are at least as bulky as piperidine, we assume that all our reactions give entirely, or almost entirely, normal product. It is noteworthy that we could not separate the isomeric piperidino-compounds related to 1 : 2-epoxyethylbenzene either by gas-chromatography (using Silicone grease on Celite) or by paper chromatography (using several different solvent mixtures for development).

The second complication is due to the possibility of consecutive reactions. This is because the product of the reaction of a secondary amine with an epoxide contains a tertiary amino-group and may, therefore, react with further epoxide:



Since our method of analysis does not distinguish between a tertiary amine and a quaternary ammonium hydroxide, we have investigated this possibility in the following manner: 1 : 2-epoxyethylbenzene was allowed to react with an excess of piperidine, and a titration at " infinite " time (at least thirty times the half-life) carried out. This must correspond to the amount of tertiary (and quaternary) base present and, if no quaternary ammonium hydroxide is formed, also to the amount of epoxide present initially. If, however, quaternary hydroxide was formed, more than one mole of epoxide would be consumed per mole of titratable base (tertiary plus quaternary) formed and the " infinity " titration would correspond to less than the initial number of moles of epoxide. In fact, we found no quaternary hydroxide to be formed.

A final complication in our system is the possibility of ethanolysis of the amines, followed by reaction of the ethoxide ion formed with the epoxide:



The incursion of this reaction will be greatest with amines which are strong enough bases to produce ethoxide ions by reaction (i), but which are sufficiently sterically encumbered for their direct reaction with epoxide to be slow. In our system the amine most likely to produce this effect is 2-methylpiperidine. We have therefore examined the product from the reaction of 2-methylpiperidine and 1 : 2-epoxyethylbenzene by gas chromatography, but can find no evidence of 2-ethoxy-1-phenylethanol (less than 1% of the total product). Since this ether is absent in this case it is reasonable to assume it to be absent in the other cases also, and hence that reactions (i) and (ii) are probably unimportant in the systems we have studied. The reaction with ethoxide ion cannot be appreciable because it would be a first-order reaction (not consuming amine or ethoxide) and would be incompatible with our observed second-order kinetics.

Experimental

Materials.—1 : 2-Epoxyethylbenzene and 1 : 2-epoxy-3-phenoxypropane (from Eastman Kodak Ltd.) were fractionated to constant refractive index through a 60 × 1·5 cm. column packed with Fenske helices, in nitrogen. The pure materials had b. p. 79·5—80°/18 mm., n_D^{25} 1·5334, and b. p. 78°/0·9 mm., n_D^{15} 1·5336, respectively. 1 : 2-Epoxy-3-phenylpropane was prepared by the method of Fourneau and Tiffeneau [7] and, when fractionated to constant refractive index as above, had b. p. 92—93°/10 mm., n_D^{20} 1·5262.

Piperidine (from Robinson Bros., Ltd., free from pyridine and tetrahydropyridine), morpholine, and 2-methylpiperidine (from Hopkin and Williams, Ltd.) were dried (NaOH, and then

[7] Fourneau and Tiffeneau, *Bull. Soc. chim. France*, 1907, **1**, 1226.

Na) and fractionated to constant refractive index. The pure materials had b. p. 105·5—105·6°/760 mm., n_D^{20} 1·4527; b. p. 129·0—129·5°/775 mm., n_D^{25} 1·4525; and b. p. 118°/750 mm., $n_D^{18·5}$ 1·4480, respectively. Diethanolamine (from British Drug Houses, Ltd.) was fractionated twice, the middle fraction being collected each time, and finally fractionally frozen, giving a product of m. p. 28° (lit.,[8] 28°). 3- and 4-Methylpiperidine (from Hopkin and Williams, Ltd.) were purified through their hydrochlorides which had m. p. 172° (lit.,[9] 171—172°) and 189° (lit.,[10] 186—189·5°) respectively. The free bases were then fractionated and had b. p. 125°/763 mm., n_D^{25} 1·4448, and b. p. 124·5°/755 mm., n_D^{25} 1·4430, respectively.

Ethanol was dried by Lund and Bjerrum's method.[11] The water content was determined by Karl Fischer titration to a conductimetric end-point, and adjusted to 0·20% w/w by addition of distilled water.

Rate Measurements.—Epoxide (~0·01 mole) was weighed into a 100 ml. graduated flask, and about 70 ml. of 99·8% ethanol were added. The flask was placed in the thermostat and at zero time the amine, in approximately equivalent amount and previously weighed into a narrow-necked flask, was added together with 99·8% ethanol to bring the volume to the mark. Aliquot parts (5 ml.) were run at appropriate intervals into a mixture of acetic anhydride (15 ml.) and acetic acid (5 ml.). The mixture was usually set aside for 2 hr. (at least 4 hr. in the case of 2-methylpiperidine): the reaction was immediately quenched thereby and the secondary amine quantitatively acetylated after 2 or 4 hr. The tertiary amine produced in the reaction, unaffected by the above treatment, was then determined by titration against perchloric acid in glacial acetic acid to a potentiometric end-point. The acetylated secondary amine is too feebly basic to affect the titration. For greater speed and accuracy the E.M.F. of the titration cell, containing silver–silver chloride and glass electrodes, was amplified by means of a valve voltmeter and read directly on a sensitive galvanometer. The end-point is then given by the single drop of perchloric acid added which causes the greatest deflection on the galvanometer. In this way a titration can be accomplished in 2—3 min., with an accuracy of 0·01 ml. of reagent added.

Synthesis of Products.—*1-Phenyl-2-piperidinoethanol.* 1-Phenyl-2-piperidinoethanol, $C_5H_{10}N·CH_2·CHPh·OH$, previously prepared from phenacylpiperidine, $C_5H_{10}N·CH_2·COPh$, by reduction with sodium and ethanol,[12] has been prepared by us by heating phenacylpiperidine (8 g., 0·04 mole) in propan-2-ol (30 g.) containing aluminium *iso*propoxide (15·5 g., 0·08 mole) for 4 hr., allowing the acetone formed to distil off. The excess of propan-2-ol was removed *in vacuo* and the base extracted with ether. 1-Phenyl-2-piperidinoethanol was obtained from the ether as prisms, m. p. 68° (lit.,[13] 68·5—69·5°) (Found: C, 76·2; H, 9·3; N, 6·5. Calc. for $C_{13}H_{19}ON$: C, 76·0; H, 9·3; N, 6·8%) [picrate, m. p. 137° (lit.,[13] 137·5°); methiodide, m. p. 137° (lit.,[12] 136—137°)]. It was identical with that prepared by heating 1 : 2-epoxyethylbenzene (10 g., 0·084 mole) with piperidine (8·8 g., 0·1 mole) in ethanol at 50° for 48 hr. After removal of solvent and excess of piperidine *in vacuo*, the product was crystallised from ethanol until it melted sharply at 69·5° (mixed m. p. 69°).

2-Phenyl-2-piperidinoethanol. Methyl piperidinophenylacetate, $C_5H_{10}N·CHPh·CO_2Me$, prepared by Klosa's method,[14] gave a *methiodide* (needles from ethanol), m. p. 151·5° (Found: C, 48·2; H, 6·0; I, 33·4. $C_{15}H_{22}O_2NI$ requires C, 48·0; H, 5·9; I, 33·8%). The ester-amine (13·2 g., 0·053 mole) was added in dry ether (20 ml.) during 1 hr. to a slurry of lithium aluminium hydride (3·4 g., 0·09 mole) in boiling ether (500 ml.). The solution was heated under reflux for a further 4 hr., after which water (100 ml.) was added. After filtration the ethereal layer was separated and dried (Na_2SO_4) and the ether removed. Distillation *in vacuo* of the residue gave *2-phenyl-2-piperidinoethanol*, b. p. 102—104°/0·002 mm., n_D^{25} 1·5434 (9·5 g., 82%) (Found: C, 76·5; H, 9·4. $C_{13}H_{19}ON$ requires: C, 76·0; H, 9·3%) [*picrate*, m. p. 140° (from slightly ethanolic water) (Found: C, 53·1; H, 5·2. $C_{19}H_{22}O_9N_4$ requires C, 52·5; H, 5·1%)]. Although this has been mentioned before [15] no method of preparation or physical constants were given.

[8] Knorr, *Ber.*, 1897, **30**, 915.
[9] Franke and Kohn, *Monatsh.*, 1902, **23**, 877.
[10] Paden and Adkins, *J. Amer. Chem. Soc.*, 1936, **58**, 2495.
[11] Lund and Bjerrum, *Ber.*, 1931, **64**, 210.
[12] Rabe and Scheider, *Annalen*, 1909, **365**, 380.
[13] Krönke, *Ber.*, 1934, **67**, 660.
[14] Klosa, *Arch. Pharm.*, 1952, **285**, 332.
[15] Thomson, Walker, and Dunn, *J. Amer. Pharm. Soc.*, 1953, **42**, 647.

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1-*Phenyl*-3-*piperidinopropan*-2-*ol*. This compound, $C_5H_{10}N{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2Ph$, prepared from 1 : 2-epoxy-3-phenylpropane by the method of Fourneau, Tréfouel, and Tréfouel,[16] crystallised from ethanol to m. p. 44·5° (Found: C, 76·5; H, 9·3. Calc. for $C_{14}H_{21}ON$: C, 76·7; H, 9·6%).

3-*Phenyl*-2-*piperidinopropan*-1-*ol*. α-Bromo-β-phenylpropionic acid,[17] b. p. 128—130°/0·1 mm., crystallised in colourless needles. It (23 g., 0·1 mole) was added to piperidine (60 g., 0·7 mole) in water (100 ml.); the solution was kept at room temperature for 1 hr., then evaporated at 60°/12 mm. The white solid was repeatedly extracted with boiling absolute ethanol until the residue no longer contained bromide ion. The residue, recrystallised from 10% aqueous ethanol, gave **β-*phenyl*-α-*piperidinopropionic acid*** (12·5 g., 61%), m. p. 213—213·5° (Found: C, 71·8; H, 8·0; N, 5·7. $C_{14}H_{19}O_2N$ requires C, 72·1; H, 8·1; N, 6·0%). The ***hydrochloride*** obtained by the action of ethanolic hydrogen chloride had m. p. 203° (Found: C, 62·3; H, 7·4; N, 5·5. $C_{14}H_{20}O_2NCl$ requires C, 62·3; H, 7·4; N, 5·2%).

By the Fischer method, this acid (10 g., 0·043 mole; dried at 100°/12 mm.), gave a glass which consisted of the hydrochlorides of the acid and its ethyl ester. The glass was dissolved in water and cooled to <10°, and ether added. 0·1N-Sodium hydroxide was slowly added until the solution was just alkaline. The ethereal layer was removed and the aqueous solution shaken twice more with ether. The combined ethereal extracts were dried (Na_2SO_4) and evaporated at 50°/12 mm.; there remained only ethyl β-phenyl-α-piperidinopropionate whose methiodide formed prisms (from ethanol), m. p. 150°. Unchanged amino-acid was recovered from the aqueous solution remaining after ether-extraction and recycled.

The ester (4 g., 0·015 mole), in dry tetrahydrofuran (20 ml.), was added during 2 hr. to a stirred slurry of lithium aluminium hydride (1·25 g., 0·03 mole) in tetrahydrofuran (50 ml.) at room temperature, and the mixture heated to 40° and stirred for a further hour. Water (50 ml.) was added, followed by ether (100 ml.). The liquid was filtered and the ethereal layer separated, dried (Na_2SO_4), and evaporated at 40°/12 mm. Crystallisation of the residue from light petroleum (b. p. 40—60°) yielded **3-*phenyl*-2-*piperidinopropan*-1-*ol*** as prisms, m. p. 48—48·5° (Found: C, 76·8; H, 9·6; N, 6·2. $C_{14}H_{21}ON$ requires C, 76·8; H, 9·6; N, 6·4%) [***methiodide*** (from ethanol), m. p. 153—153·5° (Found: C, 50·2; H, 6·7; I, 35·2. $C_{15}H_{24}ONI$ requires C, 49·8; H, 6·7; I, 35·1%); **2 : 4 : 6-*trinitrobenzenesulphonate***, needles (from ethanol), m. p. 117° (Found: C, 46·2; H, 4·8; N, 10·5. $C_{20}H_{24}O_{10}N_4S$ requires C, 46·8; H, 4·7; N, 10·9%)].

1-*Phenoxy*-3-*piperidinopropan*-2-*ol*. This compound, $C_5H_{10}N{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2{\cdot}OPh$, prepared by heating 1 : 2-epoxy-3-phenoxypropane and piperidine in ethanol at 50° (cf. Bradley, Forrest, and Stephenson [18]), formed needles (from ethanol), m. p. 54° (Found: C, 70·7; H, 9·0; N, 6·0. Calc. for $C_{14}H_{21}O_2N$: C, 71·4; H, 9·0; N, 6·0%).

3-*Phenoxy*-2-*piperidinopropan*-1-*ol*. Diethyl piperidinomalonate, $C_5H_{10}N{\cdot}CH(CO_2Et)_2$, prepared according to Jones and Wilson's method [19] for diethyl dimethylaminomalonate, had b. p. 121—122°/0·25 mm., n_D^{19} 1·4570, and gave a **2 : 4 : 6-*trinitrobenzenesulphonate***, m. p. 154—155° (Found: C, 41·1; H, 4·6. $C_{19}H_{24}O_{12}N_4S$ requires C, 40·3; H, 4·5%). The ester (24·3 g., 0·1 mole) in ether (30 ml.) was added during 1 hr. to lithium aluminium hydride (7·6 g., 0·2 mole) in boiling ether (100 ml.). The mixture was boiled for a further 6 hr., treated with water (50 ml.), and filtered. The ethereal layer was separated and the aqueous layer shaken with two further portions of ether. The combined ethereal extracts were dried (Na_2SO_4), the ether was removed, and the residue distilled; 2-piperidinopropane-1 : 3-diol (III) (4·5 g., 30%) had b. p. 156—160°/13 mm.; its **2 : 4 : 6-*trinitrobenzenesulphonate*** formed prisms (from water), m. p. 184·5° (Found: C, 37·2; H, 4·2. $C_{14}H_{20}O_{11}N_4S$ requires C, 37·2; H, 4·4%).

The diol (4 g., 0·025 mole) was treated in benzene (30 ml.) with thionyl chloride (3 g., 0·025 mole) dropwise. The precipitate crystallised when the solution was boiled for 30 min. and recrystallised from 10% aqueous ethanol as plates of ***dihydro*-5-*piperidino*-1 : 3 : 2-*dioxathiin*-2-*oxide hydrochloride*** (IV), m. p. 148° (Found: C, 40·0; H, 6·5; Cl, 15·0. $C_8H_{16}O_3NClS$ requires: C, 39·8; H, 6·6; Cl, 14·7%).

Sodium (1·58 g., 0·025 g.-atom), dissolved in phenol (30 ml.), was added to the preceding salt (3 g., 0·0125 mole) in phenol (20 ml.) and the whole kept at 60° for 12 hr. The solution was

[16] Fourneau, Tréfouel, and Tréfouel, *Bull. Soc. chim. France*, 1928, **43**, 454.
[17] Fischer, *Ber.*, 1904, **37**, 3062; Fischer and Carl, *Ber.*, 1906, **39**, 4002.
[18] Bradley, Forrest, and Stephenson, *J.*, 1951, 2877.
[19] Jones and Wilson, *J.*, 1949, 547.

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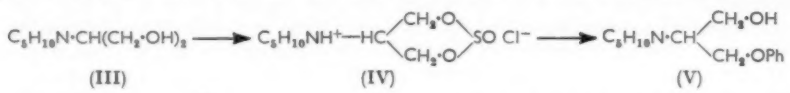
made just acid with dilute hydrochloric acid, and phenol was removed by ether (3 × 100 ml.). The aqueous solution was then made just alkaline by 0·2N-sodium hydroxide, and the precipitated base extracted with ether. Removal of the ether and distillation gave 3-phenoxy-2-piperidinopropan-1-ol (V), b. p. 120°/0·038 mm. [2 : 4 : 6-*trinitrobenzenesulphonate*,



(III) (IV) (V)

prisms (from water), m. p. 157° (Found: C, 45·4; H, 4·3. $C_{20}H_{24}O_{11}N_4S$ requires C, 45·4; H, 4·5%)].

2-*Ethoxy*-1-*phenylethanol*. 1 : 2-Epoxyethylbenzene (25 g.) was added to a solution from sodium (2 g.) in ethanol (100 ml.) and kept at 60° for 24 hr. The ethanol was removed *in vacuo*, and the residue dissolved in ether and washed with dilute sulphuric acid, sodium carbonate solution, and water. The ethereal solution was dried (Na_2SO_4), the ether removed, and the residue distilled to give 2-ethoxy-1-phenylethanol, b. p. 97—98°/0·6 mm. Gas-chromatography of this product (on Silicone resin supported on Celite) showed two closely spaced peaks, the heights and distances from the origin of which indicated that the product consisted of two components present in a ratio of ~5 : 1. These two are probably 2-ethoxy-1- and -2-phenylethanol respectively, although we have not proved this since it is not important for our purpose.

Product Analysis.—Infrared analysis. For the reaction between 1 : 2-epoxy-3-phenylpropane and piperidine infrared spectra were determined for (*a*) the actual reaction product (obtained by allowing the reaction in ethanol to go to completion and removing the ethanol and excess of piperidine *in vacuo*), (*b*) the "normal" product, 1-phenyl-3-piperidinopropan-2-ol, and (*c*) the "abnormal" product, 3-phenyl-2-piperidinopropan-1-ol. Analogous determinations were carried out for the reaction between 1 : 2-epoxy-3-phenoxypropane and piperidine, and for that between 1 : 2-epoxyethylbenzene and piperidine. All the measurements were made on carbon tetrachloride solutions with a Unicam S.P. 100 double-beam, infrared spectrophotometer.

Ethanolysis investigation. The reaction between 1 : 2-epoxyethylbenzene and 2-methylpiperidine in ethanol was allowed to go to completion and the product, after removal of ethanol and excess of amine *in vacuo*, submitted to gas-chromatography on a column of Silicone resin supported on Celite. No peak was observed at the retention time corresponding to the product of reaction of 1 : 2-epoxyethylbenzene and ethanolic sodium ethoxide (see above). The 1 : 2-epoxyethylbenzene–2-methylpiperidine product containing 3% of added ethanolysis product was also submitted to gas-chromatography: the peak due to the ethanolysis product was clearly visible. We estimate that less than 1% of ethanolysis product in our product would have been detectable.

Results

The reaction between 1 : 2-epoxyethylbenzene and piperidine at 54·75° was carried out at three different initial concentrations, and, by application of the differential method of determining reaction orders,[20] was shown to be of the first order with respect both to the epoxide and to the amine (orders 1·00 and 0·99 respectively). This was assumed to hold for the other cases also, as they all obeyed the second-order rate law:

$$dx/dt = k_2(a - x)(b - x) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

giving

$$t = \frac{2{\cdot}303}{k_2(a-b)} \log_{10} \frac{b}{a} + \frac{2{\cdot}303}{k_2(a-b)} \log_{10} \frac{a-x}{b-x}$$

where a is the initial concentration of epoxide and b is the initial concentration of amine. Values of the second-order rate constant, k_2, were determined graphically by plotting $\log_{10}[(a - x)/(b - x)]$ against t. The slope of the line is equal to $2{\cdot}303/[k_2(a - b)]$. The points all fell on good straight lines. A good proportion of the reaction was always followed, usually 10—70%, and all the runs were done in duplicate, the values of k_2 generally agreeing to better than 1%. Titrations at "infinite" time (at least thirty times the half-life) were

[20] Laidler, "Chemical Kinetics," McGraw-Hill, New York, 1950, p. 14.

TABLE 1. *Measured rate constants,* 10^4k_2 (*l. mole*$^{-1}$ *sec.*$^{-1}$).

(Figures in parentheses are temperatures in °c.)

	Piperidine	Morpholine	Diethanolamine
1 : 2-Epoxyethylbenzene	0·170 (0·00°)	0·446 (19·88°)	0·0787 (19·20°)
	1·50 (24·88)	1·47 (34·84)	0·414 (38·80)
	7·00 (44·00)	4·14 (49·28)	1·93 (60·03)
	14·8 (54·75)		
1 : 2-Epoxy-3-phenylpropane	1·54 (20·43)	1·06 (29·58)	0·129 (19·20)
	8·96 (44·22)	2·84 (44·35)	0·577 (38·84)
	16·90 (54·26)	7·18 (58·78)	2·27 (60·10)
1 : 2-Epoxy-3-phenoxypropane	3·05 (15·18)	1·31 (15·73)	0·488 (19·20)
	10·0 (29·67)	5·30 (34·41)	2·27 (38·75)
	27·7 (44·10)	20·14 (54·55)	9·43 (60·34)

	2-Methyl-piperidine	3-Methyl-piperidine	4-Methyl-piperidine
1 : 2-Epoxyethylbenzene	0·236 (24·70)	1·67 (24·65)	1·60 (24·55)
	0·863 (39·75)	5·49 (39·80)	5·21 (39·75)
	3·95 (59·75)	21·4 (59·70)	20·4 (59·70)

TABLE 2. *Rate constants interpolated to* 35°, *and Arrhenius parameters.*

(k_2 and A in l. mole^{-1} sec.$^{-1}$; E in kcal. mole^{-1}.)

	Piperidine			Morpholine			Diethanolamine		
	10^4k_2 (35°)	E	$\log_{10}A$	10^4k_2 (35°)	E	$\log_{10}A$	10^4k_2 (35°)	E	$\log_{10}A$
1 : 2-Epoxyethylbenzene	3·43	14·42	6·76	1·47	14·40	6·38	0·271	15·59	6·53
1 : 2-Epoxy-3-phenylpropane	4·63	13·81	6·45	1·54	12·97	5·39	0·436	13·60	5·27
1 : 2-Epoxy-3-phenoxypropane	14·62	13·87	7·09	5·56	13·30	6·17	1·70	14·00	6·15

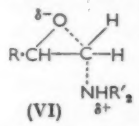
	2-Methylpiperidine			3-Methylpiperidine			4-Methylpiperidine		
1 : 2-Epoxyethylbenzene	0·579	15·64	6·86	3·80	14·45	6·83	3·67	14·25	6·67

carried out in several cases and gave values of 99·6—100·8% reaction. This shows that the reactions are irreversible and free from side-reactions.

The results are summarised in Table 1, and values of k_2 interpolated to 35°, together with the Arrhenius parameters are collected in Table 2.

DISCUSSION

Since the reactions all obey the second-order rate law and have been shown to be free from various possible complications, it is reasonable to assume that the mechanism is S_N2, involving attack of the nucleophile on the methylene group of the epoxide ring with simultaneous displacement of the ring-oxygen atom. Thus the transition state may be represented as (VI). The carbon–oxygen partial bond will be weaker than is usual in S_N2 transition states because of incomplete overlap of atomic orbitals. However, the same bond is also weaker than a normal carbon–oxygen bond in the initial state for the same reason and, to a first approximation therefore, this factor will not affect the rates. The charge separation involved in forming the transition state implies that the reactions should be strongly favoured by a change to a more powerfully solvating solvent and preliminary experiments showed that the reaction between 1 : 2-epoxyethylbenzene and piperidine was much slower in dioxan (a less strongly solvating solvent than ethanol) than in ethanol.

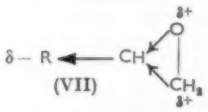


(VI)

The effect of the substituent group, R, on the rates might be expected to be different from the effect of substituent groups in S_N2 reactions of open-chain compounds. As Hinshelwood, Laidler, and Timm have shown,[21] the activation energy in such reactions can be considered approximately as being composed of two factors: (*a*) the repulsion

[21] Hinshelwood, Laidler, and Timm, *J.*, 1938, 848.

energy (energy necessary to bring up the reagent from infinity to its transition-state distance), and (*b*) the bond-stretching energy (energy necessary to stretch the C–O bond from its initial to its transition-state length). In S_N2 reactions of open-chain compounds (*e.g.*, alkyl halides) the polar effect of a substituent group on these two energy factors is in opposite directions. Thus an electron-withdrawing group will, by virtue of increasing the positive charge on the carbon atom attacked, lower the repulsion energy but increase the bond-stretching energy. The total effect is, therefore, ambiguous and the experimental results are difficult to interpret because of the simultaneous operation of a steric effect of the substituent group. In the reactions studied here, however, the polar effect of the substituent is unambiguous. An electron-withdrawing group will increase the positive charge on the carbon atom being attacked and therefore lower the repulsion energy. This increased positive charge will not greatly affect the bond-stretching energy *because the positive charge on the oxygen end of the* C–O *bond will be increased by a similar amount.* Thus if R is an electron-withdrawing group the charge situation will be as in (VII). Hence an electron-withdrawing group should, by its polar effect, facilitate the reaction. That this is so can be seen by comparing the reactions of 1 : 2-epoxy-3-phenoxypropane with those of 1 : 2-epoxy-3-phenylpropane, the phenoxymethyl group being more electron-withdrawing than benzyl and increasing the rate by a factor of 3—4.



(VII)

Since an electron-withdrawing group will increase the positive charge on the CH carbon more than that on the CH_2 carbon, it might have been expected that attack would have taken place at the former (although in this case the total effect of the substituent group on repulsion energy and bond-stretching energy would again be ambiguous). That this does not happen is no doubt due to the primary steric effects of the bulky substituent groups used here, together with the fact that the amines are all secondary and themselves, therefore, capable of producing appreciable primary steric effects.

An approximate analysis of the effect of substituent groups can be made in terms of Taft's polar and steric substituent constants σ^* and E_s.[22] Taft deduced the equation:

$$\log_{10} k - \log_{10} k_0 = \rho\sigma^* + E_s$$

where k_0 = rate of reaction of the parent compound, k = rate of reaction of a substituted derivative, σ^* = polar substituent constant, dependent only on the nature of the substituent, E_s = steric substituent constant, and ρ = reaction constant, measuring the susceptibility of the reaction to the polar effect of substituent groups. For alkaline ester hydrolysis Taft found $\rho = 2{\cdot}48$. If we assume that steric as well as polar effects of groups conform to a linear free-energy relation Taft's equation can be rewritten as:

$$\log_{10} k - \log_{10} k_0 = \rho\sigma^* + \rho' E_s$$

where ρ' is now a reaction constant measuring the susceptibility of the reaction to steric effects of substituent groups. Taking the reaction of 1 : 2-epoxypropane as standard and regarding the oxides used here as derived from 1 : 2-epoxypropane by replacement of the methyl group by phenyl, benzyl, and phenoxymethyl respectively, we may insert the values of σ^* and E_s given by Taft for these groups in the above equation, together with the values of k for the reactions with piperidine. This gives three simultaneous equations with three unknowns (k_0, ρ, and ρ') and there is, therefore, a unique solution. It must be emphasised that, because of this, our results do not in any way confirm Taft's equation. We assume the equation to hold and use the values of ρ and ρ' to give a measure of the susceptibility of the reaction to polar and steric effects of substituents, respectively. Similar calculations for the reactions with morpholine and with diethanolamine give values of k_0, ρ, and ρ' for these reactions also and the results are collected in Table 3.

[22] Taft, *J. Amer. Chem. Soc.*, 1952, **74**, 2729, 3120; 1953, **75**, 4231, 4534, 4538.

TABLE 3. *Reactions of epoxides in 99·8% ethanol at 35°*

(k_0 is the rate constant for the reaction of the parent 1 : 2-epoxypropane.)

Reagent	ρ	ρ'	$10^4 k_0$ (l. mole^{-1} sec.$^{-1}$)
Piperidine	0·8	0·2	3
Morpholine	0·9	0·2	1
Diethanolamine	0·9	0·2	0·3

Because of the frequent occurrence of deviations from linear free-energy relations, and because our measurements cover only three substituent groups, the results in Table 3 are subject to considerable uncertainty. Nevertheless it seems worthwhile to compare them with those found by Taft for the alkaline hydrolysis of esters ($\rho = 2{\cdot}48$, $\rho' = 1$). It is significant that the values of ρ for our reactions are about three times smaller than those for ester hydrolysis, where the substituent group is one carbon atom nearer the position of attack:

The values of ρ' for the reactions studied here are about five times smaller than those for alkaline ester hydrolysis, even though the amine reagents are all considerably more bulky than the hydroxide-ion reagent in ester hydrolysis. If the reagents were comparable in size to the hydroxide ion the difference in ρ' would no doubt be even greater. These results emphasise the fact that steric effects of groups often fall off more rapidly than polar effects as the substituent group is moved further from the point of attack.

The effect of varying the amine on the rates of reaction with a given epoxide has been most fully investigated for 1 : 2-epoxyethylbenzene, which has been allowed to react with six secondary amines. The rates of reaction at 25° in ethanol are compared with the basic strengths of the amines at 25° in water in Table 4. A plot of pK_a against log k is approximately linear for piperidine, morpholine, and 3- and 4-methylpiperidine. The points for

TABLE 4. *Reactions with 1 : 2-epoxyethylbenzene in ethanol at 25°.*

Amine	log k	pK_a (in water at 25°)
Piperidine	−3·824	11·13 [23]
Morpholine	−4·177	8·38 [24]
Diethanolamine	−4·886	8·88 [23]
2-Methylpiperidine	−4·625	10·87 [25] (11·15 [26], 10·98 [23])
3-Methylpiperidine	−3·775	10·92 [25] (11·14 [26])
4-Methylpiperidine	−3·796	10·89 [25]

diethanolamine and 2-methylpiperidine lie off the line, so that both these amines react more slowly than their basic strengths would suggest: this in undoubtedly due to primary steric effects, which must be of approximately the same magnitude for the reactions of these two amines since the relevant points lie an almost equal distance from the line. The introduction of a methyl group into the 3- or the 4-position of piperidine should not alter the steric requirements of the reagent and the order of rates found, 3-methylpiperidine > 4-methylpiperidine > piperidine, is what would be expected on the basis of the inductive effect of the methyl group.

The Arrhenius parameters for all the reactions studied are collected in Table 2. The energies of activation all lie within the range 13·0—14·5 kcal./mole except for the reactions of 1 : 2-epoxyethylbenzene with diethanolamine and with 2-methylpiperidine, which both have energies of 15·6 kcal./mole. The last two are the reactions of the most bulky epoxide

[23] Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3479.
[24] Ingram and Luder, *ibid.*, 1942, **64**, 3043.
[25] N. S. Isaacs, unpublished work.
[26] Horowitz and Rila, *J. Amer. Chem. Soc.*, 1958, **80**, 433.

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with the two most bulky amines and the high energies are clearly due to primary steric effects. The values of $\log_{10} A$, *i.e.*, the entropy of activation factor, vary within the range 5·27—7·09 and, because of this, it is evident that the differences in energy of activation involve changes of kinetic energy as well as potential energy and cannot, therefore, be correlated directly with structural changes. It is more rewarding in these reactions to consider structural variations in terms of changes in free energy of activation at 25° (as measured by log k for 25°) than in terms of changes in energy of activation. This has already been done in the above application of the Taft equation.

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387. *The Preparation and Physical Properties of the Pure Lutidines.*

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The preparation and purification of 2 : 3-, 2 : 4-, 2 : 5-, 3 : 4-, and 3 : 5-lutidine are described. The purities of the samples have been established by melting-point measurements. Properties which have been measured or computed are: freezing points and cryscopic constants, vapour pressure–temperature relationships, boiling points, latent heats of vaporization, densities, coefficients of expansion, refractive indices, and infrared absorption spectra.

MEASUREMENTS of certain physicochemical properties of pure 2 : 6-lutidine were recorded earlier.[1] We now give results for the less accessible 2 : 3-, 2 : 4-, 2 : 5-, 3 : 4-, and 3 : 5-dimethylpyridines. These all occur in shale-oil or coal-tar, although only the 2 : 4- and 2 : 5-lutidines are sufficiently plentiful in a commercial tar-base lutidine fraction for this to be a convenient source for their extraction on the kilogram scale.[2] The extraction of 2 : 3-lutidine is tedious and this base is perhaps more readily secured by synthesis. For the remaining 3 : 4- and 3 : 5-lutidine, there are no feasible alternatives to synthesis as a method for their preparation in quantity.

Batches of 2 : 4- and 2 : 5-lutidine were therefore prepared from a commercial " lutidine fraction, b. p. 155—161°," the first through its hydrochloride, the second through the phenol complex.[3] Some 2 : 3-lutidine was secured as a by-product of these operations through the urea complex [4] but more was synthesised by Wibaut and Kooyman's method.[5] 3 : 4-Lutidine was also synthesised by their route. The starting material for both syntheses was ethyl acetoacetate and by various improvements in the successive stages it was possible to work on a much greater scale and to increase the overall yields.

In the course of our work a commercial specimen of 3 : 5-lutidine became available. It contained non-basic and aldehydic contaminants and was probably the result of a thermal treatment of propionaldehyde–ammonia. Pure 3 : 5-lutidine obtained from it was supplemented with synthetic material made from diethyl acetonedicarboxylate by a five-stage process.[6]

An essential step in the purification of all five bases was the removal of non-basic impurities. The standard of purity required, *ca.* 99·9 moles %, was reached by fractional

[1] Biddiscombe, Coulson, Handley, and Herington, *J.*, 1954, 1957.
[2] Coulson, Hales, Holt, and Ditcham, *J. Appl. Chem.*, 1952, **2**, 71.
[3] Coulson, B.P. 715,680/1954.
[4] Milner and Y.T.D., B.P. 584,148/1947.
[5] Wibaut and Kooyman, *Rec. Trav. chim.*, 1944, **63**, 231.
[6] Coulson and Ditcham, *J.*, 1957, 356.

distillation, fractional freezing, and treatment with calcium hydride to remove traces of water, followed by distillation *in vacuo*.

The physicochemical properties which have been measured on samples of these highly purified bases or computed from measurements, are given in the Tables, and provide a basis for the characterization of pure or mixed specimens and for setting up analytical and separation techniques. Although we have compared our results with published data no useful purpose would be served by presenting a detailed collation. Many previous measurements are of lower precision, and all were made on materials of which the purity was quantitatively unknown. In general the most reliable previous values are due to Eguchi.[7]

Certain physicochemical measurements on specimens of some of these bases have already been reported from this laboratory: heats of combustion and formation;[8] solubilities in water and in deuterium oxide;[9] activity coefficients;[9] ultraviolet absorption spectra and dissociation constants;[10] vapour pressures;[11] second virial coefficients;[12] and critical temperatures.[13]

Experimental

Preparation of Pure 2 : 5-, 2 : 4-, *and* 2 : 3-*Lutidine from Tar Base Fractions.*—2 : 5-*Lutidine.* Commercial " 2 : 4–2 : 5-lutidine " contains somewhat more than 50% of the 2 : 4-isomer along with about 30—40% of 2 : 5-lutidine and smaller proportions of 2 : 3-lutidine and 2-ethyl-6-methylpyridine. The separation of a kilogram of 2 : 5-lutidine, purity 95%, from a commercial lutidine fraction was effected through the phenol complex.[2,3] Final purification was by fractional freezing, the base being kept at such a temperature that at least 24 hr. were required after seeding before 90—95% was frozen. The liquid was poured off, the crystals were melted and the process repeated until estimation showed that the required purity had been reached. The best sample of 2 : 5-lutidine so secured (593 g.) was dried by slowly distilling off about 10% in a fore-cut and the remaining portion had a purity of 99·85 moles % after distillation *in vacuo* from calcium hydride.

2 : 4-*Lutidine.* A lutidine fraction containing a known amount of the 2 : 4-isomer was diluted with twice its volume of benzene, and dry hydrogen chloride was bubbled through the mixture until the increase of weight corresponded to the transformation of the 2 : 4-isomer content into hydrochloride. The precipitated hydrochloride was filtered off and washed with benzene. The crude hydrochloride obtained in this way from commercial " 2 : 4–2 : 5-lutidine " contained hydrochlorides of other bases which were removed by recovering the bases and repeating the precipitation process, and there was some advantage in first removing the 2 : 5-isomer as the phenol complex. When hydrochloride was precipitated from a base mixture containing more than 70% of 2 : 4-isomer it could be further purified without difficulty by crystallization from alcohol to constant m. p. 214—214·5°.

Base recovered from this hydrochloride was finally purified by fractional freezing and dried by slowly distilling off a fore-cut which contained most of the water. The best specimen (500 g.) had a purity of 99·92 moles % after being dried (CaH_2).

2 : 3-*Lutidine.* As the content of 2 : 3-lutidine in tar-base lutidine fractions may be as low as 3% it is convenient to concentrate it by fractional distillation and by separation of 2 : 4- and 2 : 5-lutidine as described. To such an enriched fraction (300 g.) were added urea (340 g.) and water (300 g.) and the mixture was heated until it formed a single liquid phase. This was cooled and the 2 : 3-lutidine–urea complex which separated was crystallised twice from about one-fourth of its weight of water. It decomposed when steam-distilled and the base was recovered from the aqueous condensate. Crude 2 : 3-lutidine (80 to 90% pure) from several

[7] Eguchi, *Bull. Chem. Soc. Japan*, 1928, **3**, 227.
[8] Cox and Gundry, *J.*, 1958, 1019.
[9] Andon and Cox, *J.*, 1952, 4601; Cox, *J.*, 1952, 4606; *J.*, 1954, 3183; Andon, Cox, and Herington, *J.*, 1954, 3188; *Discuss. Faraday Soc.*, 1953, No. **15**, 168; *Trans. Faraday Soc.*, 1957, **53**, 410; Cox and Herington, *Trans. Faraday Soc.*, 1956, **52**, 926.
[10] Andon, Cox, and Herington, *Trans. Faraday Soc.*, 1954, **50**, 918.
[11] Herington and Martin, *Trans. Faraday Soc.*, 1953, **49**, 154.
[12] Andon, Cox, Herington, and Martin, *Trans. Faraday Soc.*, 1957, **53**, 1074. Cox and Andon, *Trans. Faraday Soc.*, 1958, **54**, 1622.
[13] Ambrose and Grant, *Trans. Faraday Soc.*, 1957, **53**, 771.

batches was purified by again forming and crystallizing the urea complex. When the purity had reached 95% fractional freezing was resorted to for the final purification (as with the synthetical sample, below).

Synthesis of Pure 3 : 4- *and* 2 : 3-*Lutidine.*—**3 : 4-*Lutidine.*** By allowing concentrated ammonia solution to react with ethyl α-methylacetoacetate, Wibaut and Kooyman [5] obtained a mixture of α-methylacetoacetamide and ethyl β-amino-α-methylcrotonate. The former, which remained in the aqueous ammonia, served for the preparation of 3 : 4-lutidine; the latter, which crystallized was filtered off and used for the preparation of 2 : 3-lutidine. It is preferable to avoid forming these two intermediates simultaneously, otherwise there is cross-contamination of products and loss and difficulty in succeeding stages of the two synthetic routes When ethyl α-methylacetoacetate reacted with a mixture of ammonia and ethyl cyanoacetate in aqueous solution the formation of the diammonium salt of 5-cyano-2 : 6-dihydroxy-3 : 4-dimethylpyridine (required for the further stages in the preparation of 3 : 4-lutidine) was quicker and more complete than when the reactions with ammonia and ethyl cyanoacetate were successive.

Ethyl α-methylacetoacetate, prepared [14] from ethyl acetoacetate (343 g.) but not distilled (and hence containing some ethyl acetoacetate), ethyl cyanoacetate (300 g.), and ammonia solution (1500 ml., s. g. 0·880) were mixed in a Winchester quart bottle which was stoppered and shaken for 4 or 5 days. The diammonium salt was filtered off and air-dried, the yield being 330 g. (58%). In all, 3·8 kg. of the salt were prepared and converted into 2·075 kg. of 2 : 6-dihydroxy-3 : 4-dimethylpyridine (77·8%) by Wibaut and Kooyman's method.[5] The conversion of the dihydroxy- into the dichloro-compound was effected in an autoclave on a scale one hundred times that of Wibaut and Kooyman, the yield from 2·075 kg. being 2·084 kg. (79%).

The reduction of 2 : 6-dichloro-3 : 4-dimethylpyridine to 3 : 4-lutidine was carried out with 110 g. batches of dichloro-compound, 8 g. of palladium chloride being added at the start and a further 5 g. when the reaction had slowed down after absorption of 2/3 of the stoicheiometric amount of hydrogen.

The crude 3 : 4-lutidine was freed from non-basic contaminants by blowing steam through a solution in 1·2 equiv. of 22·6% sulphuric acid.[1] The 3 : 4-lutidine (1·056 kg., 83·4% from the dichloro-derivative or 29·7% over the five stages from ethyl acetate) nevertheless still contained about 2% of γ-picoline (shown by the infrared spectrum) which was removed in a fore-cut boiling below 176°, with a fifty-plate column. The main bulk of base remaining was next subjected to a series of slow fractional freezings and a final distillation to reduce the water content.[1] The best material (775 g.) contained less that 0·05% by volume of water and after drying (CaH_2) was 99·88 moles % pure (by m. p. determination).

2 : 3-*Lutidine.* A better way of securing ethyl β-amino-α-methylcrotonate than that employed by Wibaut and Kooyman [5] is by heating ethyl α-methylacetoacetate on a steam-bath and passing in a stream of dry ammonia for 2 days. Water is formed and is separated from the reaction product which is then distilled. The fraction, b. p. 80—100°/2—3 mm., which crystallizes on cooling, is ethyl β-amino-α-methylcrotonate (77·3%). From 4·008 kg. there were obtained 4·459 kg. (68·2%) of the mono-sodium salt of ethyl 4 : 6-dihydroxy-2 : 3-dimethylpyridine-5-carboxylate following Wibaut and Kooyman's procedure.[5]

The hydrolysis and decarboxylation of the last-named compound were effected by boiling 200 g. batches with concentrated hydrobromic acid (460 ml.) for 15 hr. The reaction mixture was cooled and neutralized with aqueous sodium hydroxide; the 4 : 6-dihydroxy-2 : 3-dimethylpyridine which separated was filtered off, washed with cold water, and dried (92%).

Replacement of the two hydroxyl groups by chlorine (using $POCl_3$) is easier in 4 : 6-dihydroxy-2 : 3-dimethylpyridine than in the isomeric 2 : 6-dihydroxy-3 : 4-dimethylpyridine but the temperature must be more carefully controlled or charred by-products will result. Well-dried dihydroxy-compound (90 g.) and phosphorus oxychloride (120 ml.) in a flask fitted with a reflux condenser and guard tube were heated for 5 hr. in a metal-bath at 170—175°. The product was added to about 500 g. of crushed ice and after the exothermic reaction had subsided the mixture was warmed on the steam-bath and a small charred insoluble residue was removed by filtration. The dichloro-derivative was extracted from the filtrate with ether and the ethereal extract after being shaken with sodium carbonate solution was fractionally distilled. The

[14] Michael, *Ber.*, 1905, **38**, 2083.

TABLE 1. *Freezing constants for the six lutidines.*

Lutidine	Purity (moles %)	Depression produced by 1 mole % of impurity	Depression (K_f) for 1 mole of impurity in 1000 g.	F. p. of sample (t_f)	F. p. for 100% purity ($t_{f,0}$)
2 : 3	99·90 ± 0·02	0·467° ± 0·015°	4·95° ± 0·16°	−15·27° ± 0·02°	−15·22° ± 0·02°
2 : 4	99·92 ± 0·02	0·576 ± 0·020	6·11 ± 0·21	−64·00 ± 0·01	−63·96 ± 0·02
2 : 5	99·85 ± 0·02	0·469 ± 0·011	4·98 ± 0·12	−15·61 ± 0·01	−15·54 ± 0·02
2 : 6	99·89 ± 0·01	0·596 ± 0·026	6·32 ± 0·28	−6·16 ± 0·04	−6·10 ± 0·04
3 : 4	99·88 ± 0·01	0·710 ± 0·029	7·53 ± 0·30	−11·12 ± 0·04	−11·04 ± 0·04
3 : 5	99·91 ± 0·01	0·470 ± 0·003	4·99 ± 0·03	−6·54 ± 0·01	−6·50 ± 0·02

TABLE 2. *Vapour pressures.*

P, mm. Hg at 0° c and standard gravity; *t*, °c; $\Delta t = t$ (obs.) − t (calc.).

P	*t*	Δt	*P*	*t*	Δt
2 : 3-Lutidine					
785·29	162·412	0·000	597·63	152·203	−0·001
778·48	162·077	−0·001	543·20	148·764	−0·002
770·32	161·672	−0·001	499·93	145·829	−0·003
760·85	161·199	−0·001	444·45	141·757	+0·002
750·29	160·668	+0·002	394·32	137·704	0·000
739·67	160·125	0·000	346·46	133·429	+0·001
729·20	159·586	+0·001	298·22	128·606	0·000
720·70	159·141	0·000	248·37	122·909	+0·004
710·48	158·603	+0·001	199·57	116·337	0·000
698·06	157·940	0·000	148·25	107·822	−0·001
650·82	155·326	−0·004	109·38	99·543	−0·024
2 : 4-Lutidine					
788·89	159·825	+0·003	570·78	147·860	−0·007
773·86	159·092	+0·003	564·25	147·450	−0·006
758·50	158·333	+0·004	540·28	145·909	−0·006
748·00	157·801	0·000	463·91	140·601	−0·004
746·21	157·712	+0·001	385·60	134·371	−0·002
736·16	157·202	+0·002	339·32	130·192	+0·001
726·30	156·693	+0·001	285·18	124·673	+0·008
726·23	156·690	0·000	235·84	118·836	+0·009
715·08	156·107	−0·002	196·25	113·387	+0·018
711·07	155·900	+0·001	139·86	103·767	−0·001
708·01	155·739	+0·001	83·93	90·305	−0·018
698·46	155·232	+0·001	70·68	86·054	0·000
653·85	152·789	−0·002	46·78	76·246	−0·031
612·21	150·386	−0·004			
3 : 4-Lutidine					
783·49	180·349	0·000	599·13	169·891	−0·001
773·99	179·860	−0·001	549·14	166·617	−0·001
765·09	179·401	+0·003	500·53	163·196	0·000
762·64	179·274	+0·003	449·74	159·324	0·000
756·18	178·933	0·000	400·62	155·228	−0·001
747·75	178·487	0·000	349·24	150·485	−0·003
737·34	177·931	−0·002	300·32	145·423	+0·006
727·20	177·384	0·000	247·51	139·127	+0·001
720·78	177·035	−0·001	199·36	132·352	+0·002
707·89	176·327	+0·002	148·61	123·572	+0·005
697·77	175·761	−0·001	98·86	112·101	−0·012
651·65	173·104	−0·001			
3 : 5-Lutidine					
776·02	172·729	+0·001	546·21	159·412	−0·002
767·76	172·307	−0·002	483·05	154·971	−0·001
761·03	171·961	−0·002	449·97	152·456	−0·001
747·62	171·265	−0·004	395·94	148·007	−0·002
739·87	170·862	−0·001	344·88	143·329	−0·001
729·32	170·306	+0·001	295·09	138·193	+0·001
719·67	169·790	+0·001	248·60	132·720	+0·006
711·39	169·344	+0·002	199·77	125·975	+0·001
698·15	168·620	+0·002	152·75	118·063	+0·004
650·87	165·941	0·000	112·80	109·544	−0·014
599·51	162·850	−0·002	73·97	98·423	−0·017

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total yield (80%) from 2·426 kg. of dihydroxy-compound was 2·452 kg. of 4 : 6-dichloro-2 : 3-dimethylpyridine, b. p. 83—86°/2—3 mm. or 90—109°/4—5 mm. This dichloro-compound is dimorphic and can be obtained in an unstable crystalline form, m. p. *ca.* 20°, which is rapidly transformed on seeding into the stable form, m. p. 44·5°, described by Wibaut and Kooyman.

In the catalytic reduction of 4 : 6-dichloro-2 : 3-dimethylpyridine to 2 : 3-lutidine the method used for preparing 3 : 4-lutidine was followed. A total of 1·167 kg. of 2 : 3-lutidine was obtained (78·2%) and the yield of base over the five stages from acetoacetic ester was thus 30·3%. Its infrared spectrum showed that although it contained about 5% of α-picoline, no significant amount of any other pyridine homologue was present. This occurrence of α-picoline (and of γ-picoline in the impure synthetic 3 : 4-lutidine) was due to the ethyl α-methylacetoacetate's not being free from ethyl acetoacetate.

The final stages of purification were similar to those described for 3 : 4-lutidine, *i.e.*, removal of traces of non-basic material by blowing steam through a solution in sulphuric acid, removal of α-picoline in a fore-cut, b. p. up to 158°, with a 50-plate column, slow fractional freezing, and lastly a slow distillation with rejection of water-containing fore-cuts. The best material (628 g.) contained 0·088% v/v of water and the purity by m. p. measurements after further drying (CaH_2) was 99·90 moles %.

Purification of 3 : 5-*Lutidine.*—The commercial specimen was purified by passing steam through a boiling solution of the base in 1·2 equiv. of 22·6% sulphuric acid until samples of the base recovered from the aqueous condensate showed no traces of aldehyde in the infrared spectra. The main bulk of the purified base was then recovered from the aqueous sulphate solution and fractionally frozen until the liquid pourings showed identity in infrared spectra with the crystallized portion. The water content was then reduced to 0·07% v/v by slow distillation and removal of a water-containing fore-cut. The best specimen (850 g.) had a purity of 99·91 moles % after drying (CaH_2).

Physicochemical Measurements.—Freezing points, cryoscopic constants, and the quantitative determination of purity. The determination of purity and the measurement of the freezing point of these compounds is difficult because temperature equilibrium between liquid and solid is attained slowly. The techniques which were employed have been described elsewhere.[15,16] The purities of all the samples except 2 : 6-lutidine [1] were determined by a melting-point procedure (ref. 15, p. 19; ref. 16, p. 117). The initial freezing points and the freezing-point depressions produced by adding known quantities of impurity, 2 : 2 : 4-trimethylpentane, were determined by means of an apparatus employing a U-tube.[16] The statistical treatment of the data obtained from replicate experiments has been described.[1] The results of the measurements on the six lutidines are summarized in Table 1. Data [1] on 2 : 6-lutidine are included to complete the series. Some evidence was obtained that 3 : 4-lutidine occurs in two crystalline forms.

Vapour pressure–temperature relationships, normal boiling points, values of $(dt/dP)_{760\ mm}$, *and latent heats of vaporization.* The apparatus and techniques of measurement previously described [11,17] were used for 2 : 4-, 2 : 5-, 2 : 6-, and 3 : 4-lutidine. Measurements on 2 : 3- and 3 : 5-lutidine were made by adjusting the pressure in the apparatus to the required value and isolating the apparatus from the pumps. The barostat was not used. The b. p. of sample and water were then measured simultaneously. The time required to obtain the experimental data was reduced and it was considered that the results so obtained were more precise than the values obtained with a barostat.

Detailed results for 2 : 5- and 2 : 6-lutidines have already been published.[11] Table 2 gives the data for the other four.

Table 3 presents constants for all six lutidines; those for 2 : 5- and 2 : 6-lutidine [11] are included to complete the series. This table gives the constants in the Antoine equation, the normal boiling point, dt/dP, and the latent heat of vaporization at 760 mm. uncorrected for deviations of the vapours from the ideal-gas laws and for the molar volume of the liquid; the thermochemical calorie used is equal to 4·1840 J (abs.). It is planned to measure the virial coefficients by studying the compressibilities of the vapours, and to present corrected values of latent heats later.

Densities. Measurements of densities at 20° and 30° were made by means of a Sprengel–Ostwald pycnometer and precautions to exclude water were taken.[1] Table 4 lists the results

[15] Herington, *Analyt. Chim. Acta*, 1957, **17**, 15.
[16] Handley, *Analyt. Chim. Acta*, 1957, **17**, 115.
[17] Biddiscombe and Martin, *Trans. Faraday Soc.*, 1958, **54**, 1316.

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TABLE 3. *Constants of Antoine equation,* $\log_{10} P = A - B/(C + t)$*; normal boiling points;* $(dt/dP)_{760\ mm.}$*: and molar latent heats of vaporization.*

Lutidine	*A*	*B*	*C*	B. p. (760 mm.) (°c)	(dt/dP) at 760 mm. (°c/mm.)	Heat of vaporization at 760 mm. (uncorr.) (cal./mole)
2 : 3	7·05075 ± 0·0042	1528·935 ± 2·9	205·499 ± 0·34	161·157 ± 0·002	0·05025	9816 ± 1
2 : 4	7·11647 ± 0·0082	1564·800 ± 5·7	211·032 ± 0·62	158·403 ± 0·002	0·04984	9771 ± 3
2 : 5	7·05816 ± 0·0069	1524·016 ± 4·7	207·820 ± 0·52	157·008 ± 0·003	0·04991	9695 ± 2
2 : 6	7·05246 ± 0·0097	1467·362 ± 6·4	207·701 ± 0·72	144·045 ± 0·003	0·04818	9446 ± 3
3 : 4	7·06898 ± 0·0071	1607·874 ± 5·1	204·776 ± 0·58	179·132 ± 0·001	0·05238	10211 ± 2
3 : 5	7·08598 ± 0·0044	1593·028 ± 3·2	206·916 ± 0·36	171·910 ± 0·003	0·05148	10061 ± 1

TABLE 4. *Observed densities at 20° and 30° of the six lutidines, and calculated densities and coefficients of cubical expansion at 25°.*

$[d_{25} = 0{\cdot}5(d_{20} + d_{30});\ \alpha_{25} = 0{\cdot}2(d_{20} - d_{30})/(d_{20} + d_{30})]$

Lutidine	d_{20} (g./ml.)	d_{30} (g./ml.)	d_{25} (g./ml.)	α_{25}
2 : 3	0·94641 ± 0·00001	0·93783 ± 0·00000	0·94212	0·000911 ± 0·000001
2 : 4	0·93102 ± 0·00000	0·92226 ± 0·00000	0·92664	0·000945 ± 0·000000
2 : 5	0·92910 ± 0·00000	0·92024 ± 0·00000	0·92467	0·000958 ± 0·000000
2 : 6	0·92257 ± 0·00002	0·91355 ± 0·00002	0·91806	0·000983 ± 0·000003
3 : 4	0·95773 ± 0·00001	0·94928 ± 0·00000	0·95351	0·000886 ± 0·000001
3 : 5	0·94234 ± 0·00001	0·93377 ± 0·00000	0·93806	0·000914 ± 0·000001

TABLE 5. *Frequencies (cm.$^{-1}$) and estimates of the intensities of the main absorption peaks for liquid samples of the six lutidines.*

2 : 3-Lutidine: 4950w, 4606w, 4350sh.w, 4306w, 4233sh.w, 4108w, 4042w, 3953sh.w, 3916w, 3845w, 3775w, 3719w, 3633w, 3591w, 3453w, 3043v.s, 2978v.s, 2937v.s, 2909v.s, 2869sh.v.s, 2738w, 2651sh.w, 2607w, 2554w, 2518w, 2489w, 2426w, 2407w, 2376w, 2353w, 2310w, 2248w, 2220w, 2193w, 2159w, 2116sh.w, 2101w, 2050w, 2033w, 2000w, 1957w, 1939w, 1901w, 1870w, 1826w, 1800w, 1747w, 1708w, 1658w, 1584sh.s, 1575v.s, 1537sh.w, 1465v.s, 1449v.s, 1432v.s, 1384s, 1369s, 1315w, 1276m, 1238m, 1222sh.w, 1180s, 1165sh.w, 1123s, 1070m, 1019s, 992s, 971s, 947sh.w, 853w, 787v.s, 728v.s.

2 : 4-Lutidine: 4950w, 4640sh.w, 4572w, 4396w, 4306w, 4149w, 4029w, 3953w, 3764w, 3582w, 3472w, 3397w, 3248w, 3043sh.v.s, 3007v.s, 2944v.s, 2916v.s, 2869s, 2768w, 2726w, 2685w, 2651w, 2635w, 2549w, 2524w, 2464w, 2402w, 2358w, 2310w, 2289w, 2252sh.w, 2228w, 2212w, 2186w, 2163w, 2144w, 2126w, 2112w, 2083w, 2027w, 2007w, 1991w, 1924w, 1856w, 1760w, 1721w, 1692w, 1664w, 1629sh.m, 1604v.s, 1562v.s, 1550v.s, 1513s, 1479v.s, 1449v.s, 1397v.s, 1376s, 1294s, 1232w, 1193sh.w, 1166m, 1112w, 1037s, 995s, 976m, 951sh.w, 912s, 879m, 815v.s, 753m, 727w.

2 : 5-Lutidine: 4970w, 4640w, 4589w, 4396w, 4321w, 4177w, 4069w, 3941w, 3845w, 3764w, 3665w, 3592w, 3511sh.w, 3472sh.w, 3434w, 3406w, 3370w, 3273w, 3198sh.w, 3166sh.w, 3089m, 3021sh.s, 2992v.s, 2950v.s, 2916v.s, 2862s, 2738w, 2685w, 2623w, 2597w, 2544w, 2524w, 2474w, 2445w, 2417w, 2380w, 2336w, 2302w, 2268w, 2220w, 2155w, 2112w, 2090w, 2063w, 2030w, 2001w, 1970w, 1951w, 1930w, 1880w, 1832w, 1773w, 1738w, 1678w, 1601v.s, 1567v.s, 1490v.s, 1450v.s, 1376v.s, 1294s, 1245s, 1235w, 1215w, 1204w, 1138s, 1130s, 1043sh.s, 1031v.s, 1007sh.w, 964m, 920w, 839m, 815v.s, 727v.s, 647v.s.

2 : 6-Lutidine: 4970w, 4623w, 4365sh.w, 4306w, 4219sh.w, 4144w, 4055w, 3953w, 3775w, 3719w, 3602w, 3462w, 3406w, 3256w, 3150w, 3060v.s, 3018v.s, 2985v.s, 2957v.s, 2920v.s, 2853v.s, 2726w, 2674w, 2629w, 2575sh.w, 2539w, 2503w, 2450w, 2426w, 2407w, 2380w, 2358w, 2315w, 2298w, 2285w, 2193w, 2170w, 2094w, 2067w, 2000w, 1970w, 1945w, 1933w, 1910w, 1875w, 1816w, 1770w, 1708w, 1664w, 1643w, 1591v.s, 1578v.s, 1533s, 1511s, 1470v.s, 1451v.s, 1411sh.s, 1369s, 1326sh.w, 1278m, 1263m, 1245m, 1222s, 1153s, 1093s, 1028s, 996m, 969m, 905w, 888w, 772v.s, 728m, 716m.

3 : 4-Lutidine: 4970w, 4572w, 4396w, 4306w, 4205w, 4082w, 3953w, 3904w, 3868w, 3764w, 3612w, 3541w, 3462w, 3370w, 3273sh.w, 3089m, 3055s, 3021v.s, 3010v.s, 2971v.s, 2947v.s, 2923v.s, 2876s, 2762w, 2732w, 2685w, 2657w, 2612w, 2570sh.w, 2549w, 2474w, 2426w, 2407w, 2389w, 2376w, 2336w, 2306w, 2264w, 2244w, 2216w, 2159w, 2140w, 2097w, 2080w, 2060w, 2017w, 1988w, 1939sh.w, 1927w, 1883w, 1834w, 1776w, 1741w, 1702w, 1635m, 1594v.s, 1560s, 1492v.s, 1447v.s, 1405v.s, 1384v.s, 1349sh.w, 1305m, 1244sh.m, 1237m, 1194v.s, 1176m, 1148w, 1066s, 1048m, 1020s, 1001m, 985m, 918w, 839v.s, 821v.s, 751m, 726v.s, 600v.s.

3 : 5-Lutidine: 4970w, 4589w, 4365w, 4306w, 4247sh.w, 4191w, 4042w, 3941w, 3719w, 3561w, 3443w, 3370w, 3239sh.w, 3174w, 3029v.s, 2985 v.s, 2971sh.v.s, 2930v.s, 2869s, 2738w, 2651w, 2629w, 2612w, 2591w, 2554w, 2494sh.w, 2479w, 2445w, 2402w, 2367w, 2310w, 2268w, 2252w, 2216w, 2174w, 2137w, 2101w, 2033sh.w, 1976w, 1887sh.w, 1862w, 1776w, 1747w, 1627sh.w, 1602s, 1581v.s, 1463v.s, 1426v.s, 1379s, 1358sh.m, 1320m, 1273w, 1232s, 1164v.s, 1138s, 1043sh.s, 1032s, 1011m, 944w, 929w, 857v.s, 727sh.m, 715v.s, 710v.s.

v.s = very strong, s = strong, m = medium, w = weak, sh. = shoulder.

The approximate strengths of the bands are given with respect to liquid samples in a 0·06 mm. cell.

Frequency measurements are accurate to ±7 cm.$^{-1}$ at 3000 cm.$^{-1}$, ±2 cm.$^{-1}$ at 1500 cm.$^{-1}$, and ±1 cm.$^{-1}$ at 750 cm.$^{-1}$.

of the measurements with their standard deviations. All the samples were dried (CaH_2), and the concentration of water in the base at the end of the experiment was determined by infrared spectroscopy.[18] The concentration of water so found never exceeded 0·04% v/v and hence the error in density due to the presence of water should be less than 0·00002 g./ml.

Refractive indices. A high-accuracy Abbé refractometer (Bellingham and Stanley Ltd., London) and a sodium light source were placed in a flexible poly(vinyl chloride) glove cabinet with the two eye-pieces of the instrument projecting through holes. The cabinet was flushed with dry air. All measurements were made at 25·0 ± 0·1°, maintained by circulating water from a constant-temperature bath through the water-jacket of the refractometer. A quartz test-piece was used to check frequently the adjustment of the instrument during the series of measurements. At least ten readings were taken for each filling of the refractometer and at least five fillings were made of each lutidine, which had been dried (CaH_2). A further check was provided by measuring the refractive index of a sample of benzene 99·99 moles % pure. The value found, $1·4979_1$ for n_D^{25}, is in good accord with that given by Forziati,[19] *viz.*, 1·49792. The following values for n_D^{25} were found: 2 : 3-lutidine $1·5062_6$; 2 : 4-lutidine, $1·4983_0$; 2 : 5-lutidine, $1·4979_7$; 2 : 6-lutidine, $1·4952_4$; 3 : 4-lutidine, $1·5104_1$; 3 : 5-lutidine, $1·5037_6$.

Infrared absorption spectra. The spectra of the liquids were obtained with a double-beam prism-grating spectrometer, constructed in this laboratory.[20]

We thank Messrs. D. P. Biddiscombe, A. J. Cook, J. B. Ditcham, R. Handley, D. Harrop, W. Kynaston, D. E. Pinnock, and A. Sleven for experimental assistance. The calculations on the vapour pressure measurements for 2 : 3- and 3 : 5-lutidine were carried out in Mathematics Division, N.P.L., under the supervision of Mr. J. G. Hayes.

National Chemical Laboratory,
Teddington, Middlesex.

[*Received, January 7th*, 1959.]

[18] Coulson, Hales, and Herington, *J.*, 1951, 2125.
[19] Forziati, *J. Res. Nat. Bur. Stand.*, 1950, **44**, 373.
[20] Hales, to be published.

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388. *Ionization of Carbon–Oxygen Bonds. Part I. Ionization of Triarylmethyl Alcohols and their Alkyl Ethers in Formic Acid.*

By W. R. B. Arthur, Alwyn G. Evans, and E. Whittle.

The ionization of various substituted triphenylmethyl alcohols in formic acid has been studied spectroscopically. The results are discussed in terms of the equilibrium (1) suggested by Hammett.

Hammett [1] suggested that triphenylmethyl alcohol ionizes in formic acid as in (1). Stewart [2] has recently examined this mechanism in some detail, and studied the kinetics of the conversion of the alcohol into triphenylmethane. His paper contains a historical discussion of the reaction.

$$ROH + H{\cdot}CO_2H \rightleftharpoons R^+ + H_2O + H{\cdot}CO_2^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

We have made a similar study of the ionization of a number of substituted triphenylmethyl alcohols and some of their alkyl ethers. The kinetics of the conversion of the alcohols into the triphenylmethanes will be discussed later. Under our conditions, the solutions were quite stable during the period of the investigation.

Experimental

Formic Acid.—(*a*) " AnalaR " 98—100% formic acid (from B.D.H.), m. p. 6·9°, was purified by the anhydrous copper sulphate method,[3] followed by three fractional crystallizations. (*b*) " AnalaR " acid (from B.D.H.) was purified solely by five fractional crystallizations. (*c*)

[1] Hammett, " Physical Organic Chemistry," McGraw-Hill, New York, 1940, page 55.
[2] Stewart, *Canad. J. Chem.*, 1957, **35**, 766.
[3] Garner and Parker, *Amer. Chem. J.*, 1911, **46**, 236.

" AnalaR " 98—100% formic acid (from Hopkin and Williams), m. p. 5·1°, was treated as in (*a*) and in (*b*). All four samples had m. p. 8·2° and gave identical results in the ionization studies. (*d*) Repeated fractional crystallizations of a large volume of commercial acid yielded a product with m. p. 8·35°, but owing to the time involved in this preparation, most of the work described was done with formic acid of m. p. 8·2°.

Acetic Acid.—" AnalaR " acetic acid (2 l.) was refluxed with chromium trioxide for 12 hr., then carefully fractionated, refluxed with triacetyl borate for 12 hr., and again fractionated; the fraction of b. p. 117° was collected. The m. p. of this acid was 16·58° (lit.,[4] m. p. 16·59°).

FIG. 1*a*.

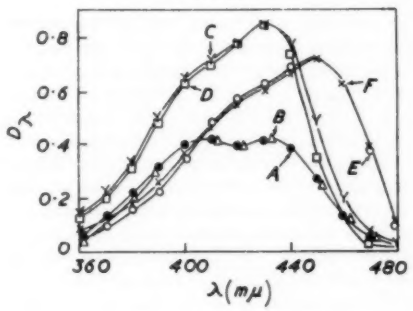


FIG. 1*b*.

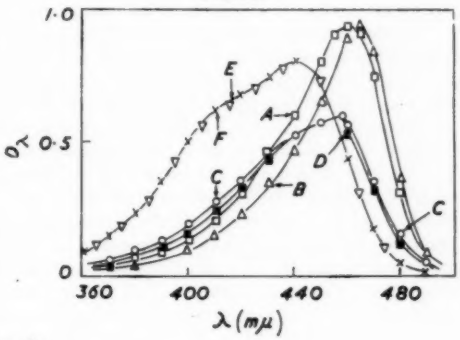


FIG. 1*a*.

A, ● 1·25 × 10^{-5}M-Triphenylmethyl alcohol in formic acid.
B, △ 1·11 × 10^{-5}M-Triphenylmethyl alcohol in 98% " AnalaR " H_2SO_4.
C, Y 2·54 × 10^{-5}M-*p*-Fluorotriphenylmethyl alcohol in formic acid.
D, □ 1·70 × 10^{-5}M-*p*-Fluorotriphenylmethyl alcohol in 98% H_2SO_4.
E, ○ 2·43 × 10^{-5}M-*p*-Bromotriphenylmethyl alcohol in formic acid.
F, × 1·53 × 10^{-5}M-*p*-Bromotriphenylmethyl alcohol in 98% H_2SO_4.

FIG. 1*b*.

A, □ 9·7 × 10^{-5}M-Tri-*p*-chlorotriphenylmethyl alcohol in formic acid.
B, △ 9·17 × 10^{-4}M-Tri-*p*-chlorotriphenylmethyl alcohol in 98% H_2SO_4.
C, ○ 4·12 × 10^{-5}M-Di-*p*-chlorotriphenylmethyl alcohol in formic acid.
D, ■ 9·38 × 10^{-6}M-Di-*p*-chlorotriphenylmethyl alcohol in 98% H_2SO_4.
E, ▽ 2·35 × 10^{-5}M-*p*-Chlorotriphenylmethyl alcohol in formic acid.
F, × 1·60 × 10^{-5}M-*p*-Chlorotriphenylmethyl alcohol in 98% H_2SO_4.

$\Delta G°$ for the ionization of tri-*p*-tolylmethyl chloride in this acid was the same as that obtained previously.[5]

Alcohols.—*p*-Methoxytriphenylmethyl alcohol was prepared by the standard method and recrystallized from light petroleum (b. p. 40—60°) and had m. p. 84° (lit.,[6] m. p. 84°). *p*-Hydroxytriphenylmethyl alcohol, prepared from benzophenone dichloride and phenol, was precipitated from ethanol as white platelets, m. p. 158° (lit.,[7] m. p. 159—160°), by addition of weak ammonia solution. *o*-Methyltriphenylmethyl alcohol was prepared by the standard method, m. p. 98° (lit.,[8] m. p. 98·5°). Di-*p*-chlorotriphenylmethyl alcohol, prepared by reaction of di-*p*-chlorobenzophenone and phenylmagnesium bromide in ether–benzene, was recrystallized from light petroleum (b. p. 40—60°) and had m. p. 86° (lit.,[9] m. p. 87°). The other triarylmethyl alcohols were prepared by normal methods and purified as described by Evans, Jones, and Osborne.[10] The m. p.s agree with their values.

Ethers of Triphenylmethyl Alcohol.—(*a*) A solution of triphenylmethyl alcohol in the appropriate alcohol was saturated with dry hydrogen chloride and refluxed for 3 hr., then set aside

[4] Eichelberger and Latter, *J. Amer. Chem. Soc.*, 1933, **55**, 3633.
[5] Evans, Price, and Thomas, *Trans. Faraday Soc.*, 1955, **51**, 4, 388.
[6] Kauffmann and Pannwitz, *Ber.*, 1912, **45**, 766.
[7] Cone and Robinson, *Ber.*, 1907, **40**, 2161.
[8] Boyde and Hatt, *J.*, 1927, 898.
[9] Stagner, *J. Amer. Chem. Soc.*, 1916, **38**, 2074.
[10] Evans, Jones, and Osborne, *Trans. Faraday Soc.*, 1954, **50**, 16, 470.

overnight, whereupon the ether crystallized. (*b*) Triphenylmethyl chloride was treated with the theoretical amount of the appropriate alcoholate in excess of the alcohol as solvent. Sodium chloride was filtered off, and the ether recrystallized from the alcohol. The ethers had m. p.: methyl, 84° (lit.,[11] 84°); ethyl, 82—84° (lit.,[12] 84—85°); isopropyl 114° (lit.,[12] 114°); benzyl, 104° (lit.,[12] 103—104°).

Spectra.—Fig. 1 shows the spectra of solutions of triarylmethyl alcohols in formic acid and " AnalaR " 98% sulphuric acid, measured on a Unicam S.P. 500 spectrophotometer. In all cases but one there is no significant difference between the shape of the spectra in the two solvents, showing the presence of triarylmethyl carbonium ions in the formic acid solution. For the exception, tri-*p*-chlorophenylmethyl alcohol, the absorption peak occurs at 465 mμ in sulphuric acid and at 460 mμ in formic acid.

Carbonium-ion Concentration.—The concentrations of the carbonium ions in the formic acid solutions have been calculated by assuming their extinction coefficients to be the same as in the 98% sulphuric acid solutions, since there is a very close similarity between the spectra of the ions in these two solvent. Justification of this assumption is provided as follows. (*a*) The percentage ionizations of these alcohols and ethers in formic acid of m. p. 8·2° are given in Table 1. No alcohol shows an ionization of greater than 105%, which supports the assumption. It is further supported by the fact that the change from mono-*p*-methyltriphenylmethyl alcohol to tri-*p*-methyltriphenylmethyl alcohol causes no increase in the ionization; this shows that these alcohols must be completely ionized since in all cases where ionization is incomplete, *e.g.*, the triarylmethyl halides in nitromethane,[10] the change in substituents from mono-*p*-methyl to tri-*p*-methyl results in a very marked increase in the ionization. (*b*) We have examined the ionization of some of these alcohols in formic acid–acetic acid mixtures. Typical plots of the optical density at the peak wavelength against the mole fraction are shown in Fig. 2. For those alcohols which we find to be 100% ionized in formic acid, the optical density increases as the

TABLE 1. *Ionization equilibria in formic acid* (*m. p.* 8·2°)

(*a*) *for* $C(C_6H_4R')(C_6H_4R'')(C_6H_4R''')\cdot OH$.

R′	R″	R‴	Ionization at 20° (%)	$-RT \ln \alpha$ (kcal. mole^{-1})	R′	R″	R‴	Ionization at 20° (%)
p-Cl	*p*-Cl	*p*-Cl	9·4	1·3	H	H	*p*-Me	104
H	*p*-Cl	*p*-Cl	23	0·7	*p*-Me	*p*-Me	*p*-Me	103
H	H	*p*-Cl	71	−0·5	H	H	*o*-Me	100
H	H	*p*-F	67	−0·4	*o*-Me	*o*-Me	*o*-Me	100
H	H	*p*-Br	63	−0·3	H	H	*p*-OMe	100
H	H	H	89	−1·1	H	H	*p*-OH	105

(*b*) for $Ph_3C\cdot OAlk$.

Alk	H	Me	Et	Pr^i	$Ph\cdot CH_2$
Ionization at 20° (%)	89	91	88	86	84

mole fraction of formic acid increases, up to a certain limit; this shows conclusively that after this point the alcohol is completely ionized. That the carbonium-ion concentration calculated for these completely ionized solutions is 100—105% (see Table 1) completely justifies our method of calculating these concentrations.

With triphenylmethyl alcohol, there is no flattening-off of the optical density–mole fraction plot, which is to be expected since it is less than 100% ionized in formic acid (see Table 1).

In Fig. 3 we give the plots of optical density at the peak wavelength–mole fraction for tri-*p*-methyltriphenylmethyl alcohol of different total alcohol concentration. By plotting the optical density corresponding to the horizontal portions (plateaux), which show 100% ionization, against carbonium-ion concentration, we have verified Beer's law for these solutions. Similar straight lines are obtained for the other completely ionized alcohols.

The carbonium-ion concentrations in solutions of the ethers in formic acid have been estimated as for the alcohols. The ethers are fully ionized in 98% sulphuric acid, and all give the same spectrum whether measured in sulphuric acid or formic acid.

[11] Hatt, *J.*, 1938, 483.
[12] Smith and Smith, *J. Amer. Chem. Soc.*, 1948, **70**, 2400.

FIG. 2.

A 2·74 × 10^{-5}M-*p*-Methoxytriphenylmethyl alcohol.
B 4·39 × 10^{-5}M-Tri-*o*-methyltriphenylmethyl alcohol.
C 2·34 × 10^{-5}M-*p*-Methyltriphenylmethyl alcohol.
D 2·09 × 10^{-5}M-*o*-Methyltriphenylmethyl alcohol.
E 1·52 × 10^{-5}M-Triphenylmethyl alcohol.

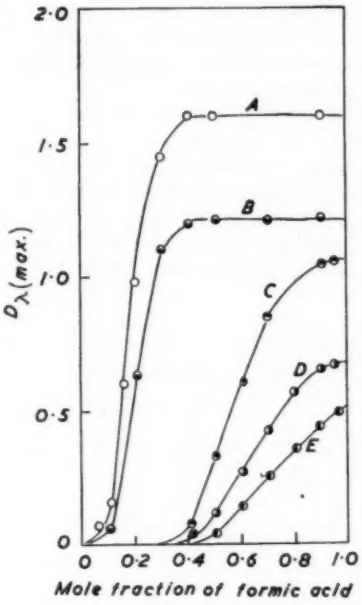
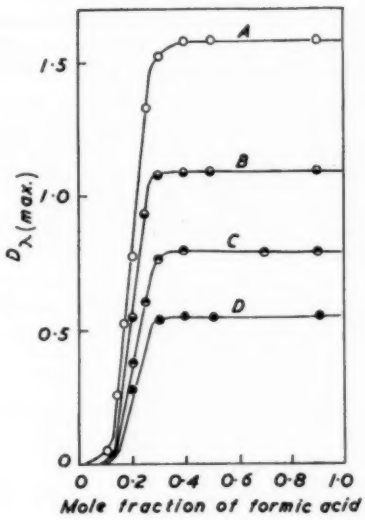


FIG. 3. *Ionization of tri-*p*-methyltriphenylmethyl alcohol in formic–acetic acid.*

A 2·02 × 10^{-5}M.
B 1·41 × 10^{-5}M.
C 1·01 × 10^{-5}M.
D 7·05 × 10^{-6}M.



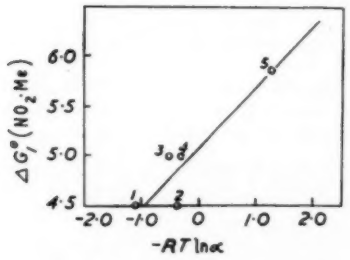


FIG. 4. *Plot of* $-RT\ln\alpha$ *for the ionization of the triarylmethyl alcohols in formic acid against* ΔG_f° *for the ionization of the corresponding chlorides in nitromethane.*

No.	R′	R″	R‴
1	H	H	H
2	*p*-F	H	H
3	*p*-Cl	H	H
4	*p*-Br	H	H
5	*p*-Cl	*p*-Cl	*p*-Cl

DISCUSSION

Nature of the Equilibrium.—If reaction (1) correctly represents the ionisation of the triarylmethyl alcohols in formic acid, then the equilibrium constant, K_1, may be written

$$K_1 = \alpha[H_2O][H{\cdot}CO_2^-]/[H{\cdot}CO_2H] \text{ where } \alpha = [R^+]/[ROH]$$

The carbonium-ion concentration $[R^+]$ plotted against the concentration of un-ionized alcohol [ROH] gave good straight lines in all cases. Similar results are obtained for the ethers. α is therefore independent of alcohol concentration for any given alcohol. This behaviour is not predicted by reaction (1). However, our data are compatible with Hammett's equation if the remaining terms in the expression for K_1 do not change with alcohol concentration. Since the ionization occurs in formic acid, it is only necessary to

consider changes in the concentrations of water and formate ion. The water concentration in formic acid of m. p. 8·2° is approximately 9×10^{-2} mole $l.^{-1}$, while the formate-ion concentration, as Stewart has pointed out, is at least 10^{-3} mole $l.^{-1}$. Both these concentrations are much larger than that of the original alcohol ($\sim 10^{-5}$ mole $l.^{-1}$), so that the amounts of water and formate ion produced by reaction (1) are negligible, and hence reaction (1) is compatible with the observed constancy of α.

The validity of reaction (1) can be checked by investigating the variation of α with variation of formate-ion concentration and water concentration. According to our expression for K_1, $1/\alpha$ should be proportional to the formate-ion concentration. Stewart has shown that this is so over a considerable range of concentration of formate ion, added in the form of sodium formate.

We have examined the variation of α when water is added to solutions of the alcohols in formic acid of m. p. 8·2°. Those which were completely ionized in this acid showed no change in ionization even when the added water had reduced the m. p. of the formic acid to 3·0°. The effect of added water on the incompletely ionized alcohols is shown in Table 2; $1/\alpha$ is approximately proportional to $[H_2O]^{1.8}$, whereas reaction (1) would require a first-power dependence on water concentration.

TABLE 2. *Ionization in wet formic acid* (*all* para-*substituents*).

R′	R″	R‴	M. p.*	$[H_2O]$(M)†	Iontn.‡	x§	R′	R″	R‴	M. p.*	$[H_2O]$(M)†	Iontn.‡	x§
H	H	H	2·95°	2·41	9·4		Cl	Cl	H	3·50	2·19	0·7	
			5·10	1·46	30·5	1·74				5·60	1·24	2·2	1·80
			6·90	0·66	60					7·31	0·49	11·4	
			8·20	0·088	89					8·20	0·088	23	
Br	H	H	5·10	1·46	7·5		Cl	Cl	Cl	5·38	1·34	0·38	
			6·90	0·66	26	1·74				6·45	0·86	0·78	1·85
			8·20	0·088	63					7·30	0·45	2·75	
Cl	H	H	2·95	2·41	2·8					8·20	0·088	9·4	
			5·60	1·24	9·3	1·76							
			7·30	0·49	35								
			8·20	0·088	71								

* M. p. of formic acid. † The acid of m. p. 8·35° being assumed anhydrous. ‡ Ionization at 20° (%). § Order in water.

There are, however, two other equilibria to be considered, both of which provide formate ions:

$$H{\cdot}CO_2H + H_2O \rightleftharpoons H_3O^+ + H{\cdot}CO_2^- \quad . . . . . (2)$$

$$H{\cdot}CO_2H + H{\cdot}CO_2H \rightleftharpoons H{\cdot}CO_2H_2^+ + H{\cdot}CO_2^- \quad . . . . . (3)$$

Both lie well to the left so that in Stewart's experiments very little of the added formate ion could be removed by either reaction's going still further to the left. Hence only reaction (1) is important and $1/\alpha$ is proportional to $[H{\cdot}CO_2^-]$ as observed.

On the other hand, the addition of water to the system not only suppresses the ionization of the alcohol according to reaction (1), but also has the secondary effect of increasing the $[H{\cdot}CO_2^-]$ according to reaction (2), which also reduces the alcohol ionization. Thus the order in water should be greater than unity. If reaction (3) may be neglected as a source of formate ion, then, assuming $[H_3O^+] = [H{\cdot}CO_2^-]$, we can show that

$$K_1/\sqrt{K_2} = \alpha[H_2O]^{1.5}/[H{\cdot}CO_2H]^{0.5}$$

The exponent 1·5 agrees moderately well with the observed value of 1·8. The data available do not seem reliable enough to calculate accurately the relative contributions of formate ion from reactions (2) and (3). For the incompletely anhydrous formic acid (m. p. 8·2°) used, it seems likely that reaction (2) provides about three times as much formate ion as reaction (3). This is almost certainly a lower limit. Consequently reaction (3) will have little effect.

XUM

It might be suggested that the order 1·8 found for water is due to a change in the activity coefficient of the water with change in its concentration. We have carried out experiments on the depression of the freezing point of formic acid by water over most of the range involved. The "*i*"-factors (in parentheses following molar concentrations of water) are 0·147 (0·97), 0·269 (0·94), 0·593 (0·97), 0·877 (0·90), 1·674 (0·92), and their slight decrease over this range could not account for the order of 1·8 for the effect of water on the ionisation.

As regards the ethers, R·OAlk, the analogue of reaction (1) would be:

$$R{\cdot}OAlk + H{\cdot}CO_2H \rightleftharpoons R^+ + HO{\cdot}Alk + H{\cdot}CO_2^- \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Since the water concentration, 9×10^{-2} mole l.$^{-1}$, in 8·2° m. p. formic acid, is much greater than the H·OAlk concentration can possibly be (maximum [H·OAlk] = 10^{-4} mole l.$^{-1}$), the carbonium ions produced in reaction (4) will rapidly equilibrate with the water present to give a state of affairs which will be little different from that of the corresponding alcohol, ROH, in formic acid. This is borne out by the fact that the percentage ionizations for the ethers of triphenylmethyl alcohol are practically the same as that for triphenylmethyl alcohol itself (see Table 1).

Equilibrium Constants.—It has been shown that, under our experimental conditions, the terms other than α in the expression for K_1 may be presumed constant, particularly as the same formic acid was used in all cases. Hence the value of α may be used as a measure of K_1, and $RT \ln \alpha$ as a measure of $\Delta G_1°$.

TABLE 3. *Effect of temperature on ionization of* para-*substituted triarylmethyl alcohols.*

R′	R″	R‴	Temp. (°) (α)				$\Delta H_1°$	$\delta(\Delta H_1°)$ (kcal. mole^{-1})	$\delta(-RT \ln \alpha)$
Cl	Cl	Cl	18·5 (0·105)	43·0 (0·166)	60·0 (0·23)	75·2 (0·31)	4·0	(0)	(0)
H	Cl	Cl	18·2 (0·32)	44·5 (0·48)	56·4 (0·69)	69·4 (0·76)	3·2	0·8	0·6
H	H	Cl	21·0 (2·2)	47·2 (2·9)	56·0 (3·9)	65·5 (3·5)	1·9	1·3	1·2
H	H	Br	22·0 (1·8)	46·0 (2·1)	56·4 (2·6)	68·5 (3·0)	2·2	−0·3	−0·2

The main interest centres on those alcohols which are not completely ionized at room temperature. Their behaviour is similar to that of the corresponding chlorides in nitromethane as is shown in Fig. 4, in which $RT \ln \alpha$ is plotted against the free-energy change for the ionization of the corresponding chlorides in nitromethane. The only exception is the *p*-fluoro-compound where it is possible that ionization of the C–F bond may introduce complications.

From the variation of $RT \ln \alpha$ with temperature for the incompletely ionized alcohols, relative values of $\Delta H_1°$ can be determined. The results are in Table 3. All these alcohols react slowly with formic acid at the higher temperatures, but in all cases the values were obtained by extrapolation to zero time. It was shown that the shape and intensity of the light-absorption curve do not vary over the temperature range used. The change in $\Delta H_1°$ is equal to the change in $(-RT \ln \alpha)$, *i.e.*, to the change in $\Delta G_1°$. This means that the entropy change for the ionization is not affected by the change in the nature and the number of the *para*-substituents. This would be expected since the solvation shell for the ion will be far removed from the *para*-position.

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389. *The Activation of Carbon–Carbon Double Bonds by Cationic Catalysts. Part VII.* Dimerization of* 1 : 1-*Diphenylethylene to* 1 : 1 : 3 : 3-*Tetraphenylbut*-1-*ene in the System Benzene–Stannic Chloride–Hydrogen Chloride.*

By Alwyn G. Evans and J. Lewis.

Dimerization of 1 : 1-diphenylethylene in benzene–stannic chloride–hydrogen chloride has been studied dilatometrically. The initial rate of dimerization is of first order with respect to both stannic chloride and hydrogen chloride, no reaction occurring in the absence of either. Non-reacting systems are colourless, but reacting systems have an absorption spectrum similar to that given by this olefin dimerizing in benzene–stannic chloride–water.[1]

Earlier Parts reported the dimerization of 1 : 1-diphenylethylene and its derivatives with use of trichloroacetic acid, iodine, and stannic chloride–water as catalysts. This work has now been extended by using stannic chloride–hydrogen chloride as catalyst.

Experimental

Materials.—Stannic chloride was prepared by the electrolysis of fused anhydrous stannous chloride under high-vacuum conditions (Part V [1]). Benzene and 1 : 1-diphenylethylene were purified by the rigorous methods described in Part V.[1] Hydrogen chloride was prepared by the action of "AnalaR" concentrated sulphuric acid on "AnalaR" ammonium chloride, and collected at about 700 mm. Hg pressure in a Pyrex glass apparatus which had been baked out under a high vacuum. Sections of this apparatus could be isolated by closing taps lubricated with "Apiezon" grease, and the gas was purified by condensation and evaporation from vapour traps cooled alternately by liquid nitrogen and by solid carbon dioxide–acetone, the system being pumped out each time the hydrogen chloride was solidified. The pure gas was admitted through long capillary stems to a series of glass bulbs of various known capacities. When the gas had attained the laboratory temperature, the pressure, measured by a mercury manometer, was adjusted to about 700 mm. Hg, and the bulbs were sealed off at graduation marks on the capillary stems.

Procedure.—The bulbs containing known amounts of hydrogen chloride were fused to the ends of the stems of dilatometers. The hydrogen chloride bulbs were provided with fragile, sealed capillaries which could be shattered by iron-in-glass breakers when it was required to transfer the gas to the dilatometer. The dilatometers were filled, through side tubes joined to the stems, with known amounts of 1 : 1-diphenylethylene, stannic chloride, and benzene, by use of the high-vacuum technique, method A, described in Part V.[1] The filled dilatometers were separated, each with its hydrogen chloride bulb, by sealing off at the side tubes. The connecting capillaries were shattered by impact from the breakers, and the hydrogen chloride was withdrawn into the dilatometers by immersing the dilatometer bulbs in liquid nitrogen, and the filling tubes together with the empty hydrogen chloride bulbs were removed by sealing off near the tops of the dilatometer stems. Dilatometers were filled in this way with solutions having various known concentrations in 1 : 1-diphenylethylene, stannic chloride, and hydrogen chloride. In some instances, optical cells were filled jointly with the dilatometers.

The dilatometers and optical cells were kept at 30·3°, 39·9°, and 55·0° in thermostats (±0·05°). The volume changes were followed in the dilatometers, and the rate of volume change was converted into mole $l.^{-1}$ $sec.^{-1}$ of dimer produced as described in Parts I [2]a nd II,[3] by using the following values for the volume change accompanying the complete conversion of 1 mole of monomer into ½ mole of dimer: 11·95 ml. at 30·3°, 11·70 ml. at 39·9°, and 12·60 ml. at 55·0° (see Part V [1]). The spectra were measured in the optical cells by a Unicam S.P. 500 spectrophotometer.

* Part VI, Evans, Jones, and Thomas, *J.*, 1958, 4563.

[1] Evans and Lewis, *J.*, 1957, 2975.
[2] Evans, Jones, and Thomas, *J.*, 1955, 1824.
[3] Evans, Jones, Jones, and Thomas, *J.*, 1956, 2757.

XUM

Results

In the absence of hydrogen chloride, systems containing rigorously purified benzene, olefin, and stannic chloride reacted at a negligible rate (Fig. 1, curve *A*). On introduction of hydrogen chloride to such a system a great increase in the reaction rate was observed (Fig. 1, curve *A'*). No volume change occurred when hydrogen chloride was admitted to similar systems in the absence of stannic chloride, or when the monomer was omitted. It is evident, therefore, that hydrogen chloride is a cocatalyst for this reaction of the monomer. Systems containing benzene, olefin, stannic chloride, and hydrogen chloride were found, within the limits of the concentrations

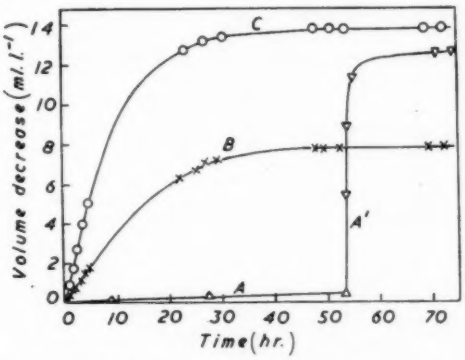
FIG. 1. *Volume change during reaction at* 39·9°.

Curve *A* [Initial monomer] 1·33 mole l.$^{-1}$. [Stannic chloride] 4·90 × 10^{-3} mole l.$^{-1}$.

Curve *A'* As *A* with hydrogen chloride (5·12 × 10^{-2} mole l.$^{-1}$) added.

Curve *B* [Initial monomer] 0·84 mole l.$^{-1}$. [Stannic chloride] 5·49 × 10^{-3} mole l.$^{-1}$. [Hydrogen chloride] 4·00 × 10^{-2} mole l.$^{-1}$.

Curve *C* [Initial monomer] 1·40 mole l.$^{-1}$. [Stannic chloride] and [hydrogen chloride] as *B*.



used, to give reaction curves (Fig. 1; curves *A'*, *B*, and *C*) similar to those obtained in the water-cocatalysed reaction (Part V), the volume decreasing until a constant value was obtained. As in the previous work, the product of the reaction, separated as described in Part I,[2] was found to be solely 1 : 1 : 3 : 3-tetraphenylbut-1-ene (cf. Schoepfle and Ryan [4]); agreement between the amount of dimer obtained from the equilibrium solutions and that expected from the observed volume change was again within the limits ±5%. Initial rates of reaction were found from the initial slopes of the reaction curves, and the dependence of rate on concentration of hydrogen chloride, for a set of fixed concentrations of stannic chloride and constant initial olefin concentration, is shown in Table 1. Initial rates of dimerization in absence of hydrogen chloride are negligible, and the initial rates vary linearly with hydrogen chloride concentration over

TABLE 1. *Variation in initial rate at* 39·9° *with monomer, stannic chloride, and hydrogen chloride concentrations.*

[Initial monomer] (mole l.$^{-1}$)	[Stannic chloride] (10^{-3} mole l.$^{-1}$)	[Hydrogen chloride] (10^{-3} mole l.$^{-1}$)	Initial rate of dimer formation (10^{-3} mole l.$^{-1}$ hr.$^{-1}$)	[Initial monomer] (mole l.$^{-1}$)	[Stannic] chloride] (10^{-3} mole l.$^{-1}$)	[Hydrogen chloride] (10^{-3} mole l.$^{-1}$)	Initial rate of dimer formation (10^{-3} mole l.$^{-1}$ hr.$^{-1}$)
1·33	11·2	Nil	1·9	1·33	2·35	Nil	0·3
1·33	11·2	8·40	17·1	1·33	2·35	3·85	2·14
1·33	11·2	12·5	27·4	1·33	2·35	7·99	2·99
1·33	11·2	23·5	48·7	1·33	2·35	10·2	4·92
1·33	5·49	Nil	0·5	0·85	14·9	57·2	68·4
1·33	5·49	5·72	5·69	1·40	14·9	57·2	169·0
1·33	5·49	10·4	9·40	1·96	14·9	57·2	363·0
1·33	5·49	27·1	29·9				
1·33	5·49	40·5	41·9	1·33	2·35	10·0	4·52
				1·33	5·49	10·0	10·7
				1·33	11·2	10·0	21·1

the considerable range for which these rates have been determined. There is no optimum [HCl]/[$SnCl_4$] ratio as was found for the [H_2O]/[$SnCl_4$] ratio.[1] Using the results of Table 1 we have plotted log (initial rate) against log [initial monomer] for constant [stannic chloride]

[4] Schoepfle and Ryan, *J. Amer. Chem. Soc.*, 1930, **52**, 4021.

and constant [hydrogen chloride]; log (initial rate) against log [stannic chloride] for constant [initial monomer] and constant [hydrogen chloride]; and log (initial rate) against log [hydrogen chloride] for constant [initial monomer] and constant [stannic chloride]. We find the orders in monomer, stannic chloride, and hydrogen chloride to be, respectively: $2{\cdot}0 \pm 0{\cdot}3$, $1{\cdot}0 \pm 0{\cdot}1$, and $1{\cdot}0 \pm 0{\cdot}2$.

The concentrations of monomer and dimer at equilibrium, $[M]_e$ and $[D]_e$, have been obtained for solutions of different monomer concentrations as described in Part I [2] (see Table 2). If we plot log $[D]_e$ against log $[M]_e$, we obtain a straight line of slope $2{\cdot}2 \pm 0{\cdot}2$, showing that $[D]_e/[M]_e^2 = K$. The equilibrium constants, K, are independent of the concentrations of

FIG. 2(*a*) *Spectrum of system given in Fig.* 1, *curve A.*

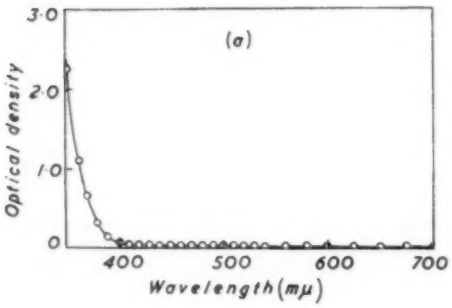
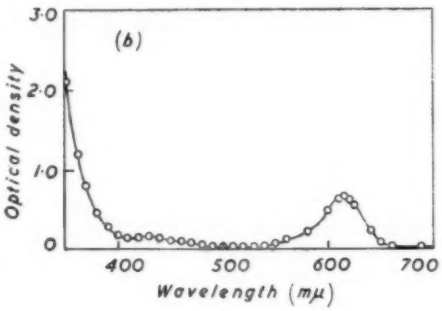


FIG. 2(*b*) *Spectrum of system given in Fig.* 1, *curve A'.*



stannic chloride and of hydrogen chloride (see Table 3). Mean values of K are given for the three temperatures in Table 4, and the plot of log K against $1/T$ has been used to find the exothermicity of the reaction: the value obtained ($-\Delta H°$) from the slope of this line is $10{\cdot}3 \pm 0{\cdot}5$ kcal. mole^{-1} (see Table 4). The values of $\Delta G°$ and $\Delta S°$ for this dimerization are also given in Table 4.

As in our study of the water-cocatalysed reaction (Part V [1]), we have examined the spectra of the solutions in the absence and in the presence of the cocatalyst, and again we find that

TABLE 2. $[M]_e$ *and* $[D]_e$ *at* 39·9°.

$[M]_e$ (M)	$[D]_e$ (M)	Slope of log $[D]_e$–log $[M]_e$ plot
0·170	0·339	
0·220	0·589	$2{\cdot}2 \pm 0{\cdot}2$
0·260	0·856	

TABLE 3.

Temp.	[Initial monomer] (mole l.$^{-1}$)	[Stannic chloride] (10^{-3} mole l.$^{-1}$)	[Hydrogen chloride] (10^{-3} mole l.$^{-1}$)	K (mole^{-1} l.)
39·9°	1·33	11·2	8·4	11·9
39·9	1·33	11·2	23·5	12·4
39·9	1·33	5·49	10·4	12·3 (Mean 12·2)

TABLE 4. *Dimerisation of* 1 : 1-*diphenylethylene to* 1 : 1 : 3 : 3-*tetraphenylbut*-1-*ene in stannic chloride–hydrogen chloride–benzene.*

k_f * (mole^{-2} l.^{2} sec.$^{-1}$)	E_f (kcal. mole^{-1})	K (mole^{-1} l.)
$2{\cdot}3 \times 10^{-2}$ (30·3°)	$4{\cdot}7 \pm 0{\cdot}5$	$20{\cdot}1 \pm 0{\cdot}5$ (30·3°)
$3{\cdot}1 \times 10^{-2}$ (39·9°)		$12{\cdot}2 \pm 0{\cdot}5$ (39·9°)
$4{\cdot}3 \times 10^{-2}$ (55·0°)		$5{\cdot}5 \pm 0{\cdot}2$ (55·0°)

* k_f is expressed in terms of the number of moles per l. of dimer appearing per second.

$\Delta G_f^{\ddagger}$ (kcal. mole^{-1})	$\Delta H_f^{\ddagger} = (E_f - RT)$ (kcal. mole^{-1})	$\Delta S_f^{\ddagger}$ (cal. deg.$^{-1}$ mole^{-1})	$\Delta G°$ (kcal. mole^{-1})	$\Delta H°$ (kcal. mole^{-1})	$\Delta S°$ (cal. deg.$^{-1}$ mole^{-1})
20·1 (30·3°)	4·1	−52·8 (30·3°)	−1·8 (30·3°)	−10·3	−28·0 (30·3°)

addition of the cocatalyst to the colourless solutions of monomer and stannic chloride in benzene not only brings about reaction but is marked by a change in the spectrum to give absorption in the violet end of the visible region and a peak in the 600 mμ region (see Fig. 2*b*).

Activation Energy for the Stannic Chloride–Water System.—The results given in Part V for the stannic chloride–water system have now been extended to include the rate constants for this reaction at 30·3°, 39·9°, and 55·0°. The values are given in Table 5 and the activation energy E_t obtained from these is 7·9 kcal. mole^{-1}.

TABLE 5. *Dimerisation of* 1 : 1-*diphenylethylene to* 1 : 1 : 3 : 3-*tetraphenylbut*-1-*ene in stannic chloride–water–benzene.*

k_t * (mole^{-2} l.^{2} sec.$^{-1}$)	E_t (kcal. mole^{-1})	K (mole^{-1} l.)
$6{\cdot}8 \times 10^{-3}$ (30·3°)	7·9 ± 0·2	19·9 ± 0·4 (30·3°)
$9{\cdot}9 \times 10^{-3}$ (39·9°)		11·2 ± 0·4 (39·9°)
$18{\cdot}2 \times 10^{-3}$ (55·0°)		5·4 ± 0·2 (55·0°)

* k_t is expressed in terms of the number of moles per l. of dimer appearing per second.

$\Delta G_t^{\ddagger}$ (kcal. mole^{-1})	$\Delta H_t^{\ddagger} = (E_t - RT)$ (kcal. mole^{-1})	$\Delta S_t^{\ddagger}$ (cal. deg.$^{-1}$ mole^{-1})	$\Delta G°$ (kcal. mole^{-1})	$\Delta H°$ (kcal. mole^{-1})	$\Delta S°$ (cal. deg.$^{-1}$ mole^{-1})
20·7 (30·3°	7·3	−44·2 (30·3°)	−1·8 (30·3°)	−10·5	−28·7 (30·3°)

The values of K, $\Delta G°$, $\Delta H°$, and $\Delta S°$ are taken from Part V.

DISCUSSION

1 : 1-Diphenylethylene is not dimerized by stannic chloride in benzene unless a cocatalyst is present. This was shown in Part V, where water as co-catalyst was studied. The present work shows that hydrogen chloride is also a co-catalyst in this reaction, although, in the absence of stannic chloride, it does not polymerize or react with the monomer.

Any mechanism for the dimerization of 1 : 1-diphenylethylene in benzene–stannic chloride–hydrogen chloride systems must account for the following observations. The initial rate of dimerization is of (*a*) second order in monomer, (*b*) first order in stannic chloride, (*c*) first order in hydrogen chloride; also (*d*) the order in catalyst is the same in the forward and the reverse direction (since $[D]_e/[M]_e^2 = K$, independent of the catalyst concentration).

We postulate the following mechanism where M = monomer, and D = dimer:

$$M + SnCl_4 + HCl \underset{b}{\overset{a}{\rightleftharpoons}} HM^+(SnCl_5)^- \quad \ldots\ldots\ldots\ldots (1)$$

$$M + HM^+(SnCl_5)^- \underset{b}{\overset{a}{\rightleftharpoons}} HD^+(SnCl_5)^- \quad \ldots\ldots\ldots\ldots (2)$$

$$HD^+(SnCl_5)^- \underset{b}{\overset{a}{\rightleftharpoons}} D + SnCl_4 + HCl \quad \ldots\ldots\ldots\ldots (3)$$

This mechanism will account for the results if we make the same assumption as in Part V that reaction (2*a*) is the rate-controlling step. Then the initial rate of dimerization, as observed experimentally, is given by:

$$\text{Initial rate} = k_{2a}[HM^+(SnCl_5)^-][M]$$
$$= k_{2a}(k_{1a}/k_{1b})[SnCl_4][HCl][M]^2$$

This expression is consistent with our results, and the velocity constant, k_t, for the dimerization has been evaluated from the expression:

$$\text{Initial rate} = k_t[SnCl_4][HCl][M]^2$$
$$\text{where } k_t = k_{2a} \cdot k_{1a}/k_{1b} = k_{2a}K_1$$

This constant is given for each temperature in Table 4. From these values of k_t, the corresponding activation energy, E_t, was calculated and found to be 4·7 kcal. mole^{-1}. The

values of K, $\Delta G°$, $\Delta H°$, and $\Delta S°$ obtained for this dimerization (see Table 4) are in good agreement with those obtained in our previous work on the dimerization of 1 : 1-diphenylethylene with trichloroacetic acid in benzene [2] and in nitroethane; [3] with iodine in β-nitropropane; [5] and with stannic chloride–water in benzene.[1]

The stannic chloride–hydrogen chloride catalysed reaction differs from the stannic chloride–water catalysed reaction in the following ways: (*a*) The velocity constant of the HCl-cocatalysed reaction is greater than that of the H_2O-cocatalysed reaction. The activation energy for the dimerization is reduced from 7·9 kcal. mole^{-1} to 4·7 kcal. mole^{-1} on changing from water to hydrogen chloride. The effect of this decrease of 3·2 kcal. mole^{-1} on the rate of reaction is partly offset by an accompanying decrease in the entropy of activation (see Tables 4 and 5).

(*b*) There is no optimum $[HCl]/[SnCl_4]$ ratio as there is for the $[H_2O]/[SnCl_4]$ ratio. This means that no stable stannic chloride–hydrogen chloride complex is formed. Either the proton transfer occurs in a 3-body reaction as given in equation (1), or, which is practically the same, an equilibrium may exist of the type:

$$SnCl_4 + HCl \underset{b}{\overset{a}{\rightleftharpoons}} SnCl_4,HCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

which lies well to the left, followed by the proton transfer:

$$SnCl_4,HCl + M \underset{b}{\overset{a}{\rightleftharpoons}} MH^+SnCl_5^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

In this case:

$$\begin{aligned} \text{Initial rate} &= k_{2a}[HM^+(SnCl_5)^-][M] \\ &= k_{2a}(k_{5a}/k_{5b})[SnCl_4,HCl][M]^2 \\ &= k_{2a}(k_{5a}/k_{5b})(k_{4a}/k_{4b})[SnCl_4][HCl][M]^2 \\ \text{and } k_t &= k_{2a}(k_{5a}/k_{5b})(k_{4a}/k_{4b}) = k_{2a}K_5K_4 \end{aligned}$$

In related work on hydrogen chloride–aluminium chloride complexes, Brown and Pearsall [6] could find no evidence for the existence of the corresponding complex $HAlCl_4$, although in the presence of aromatic hydrocarbons, ternary complexes of great stability are formed which correspond in properties to salts of a very strong acid having the composition of this hypothetical complex.

(*c*) There is no evidence of solvation of the ion pairs by the catalyst, as there is when water is the cocatalyst. The fact that a stannic chloride–hydrogen chloride complex does not exist in these systems, or, if it does, is present in very small concentrations, whereas evidence for a stable $SnCl_4,2H_2O$ complex is found in the stannic chloride–water system, shows that the attraction between chlorine and $SnCl_4$ is much less than between oxygen and $SnCl_4$. It is not surprising then that although $SnCl_4$ solvates the $MH^+(SnCl_4,H_2O\ OH)^-$ ion pair, it does not solvate the $MH^+(SnCl_5)^-$ ion pair. It is also found that although $SnCl_4,2H_2O$ helps to solvate the $MH^+(SnCl_4,H_2O\ OH)^-$ ion pair there is no evidence for solvation of the $MH^+(SnCl_5)^-$ by $SnCl_4,HCl$. This is to be expected since the acid $SnCl_4,2H_2O$ will form hydrogen bonds with the $(SnCl_4,H_2O\ OH)^-$ ion, but one would not expect hydrogen bonding between $SnCl_4,HCl$ and the $SnCl_5^-$ ion.

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UNIVERSITY COLLEGE, CATHAYS PARK, CARDIFF. [*Received, January 12th,* 1959.]

[5] Evans, Jones, and Thomas, *J.*, 1957, 2095.
[6] Brown and Pearsall, *J. Amer. Chem. Soc.*, 1951, **73**, 4681.

390. *The Structure of Lecithin Micelles in Benzene Solution.*

By P. H. Elworthy.

Diffusion coefficients of lecithin in benzene were determined by using the Gouy diffusiometer. Integral measurements yielded patterns which were characteristic of two-component diffusion, from which the mean molecular weight of the small micelles was determined. In semi-differential diffusion measurements the interference patterns complied with the theory for diffusion of a single solute, and the molecular weight of the large micelles was determined from these measurements. Viscosity studies showed that the large micelles were asymmetric, and treatment as ellipsoids gave axial ratios of about 2 : 1. The final molecular weights for the large and the small micelles agreed with those obtained from osmotic data. The properties of solutions of model structures were calculated and compared with the observed properties; this indicated that the micelles had a laminar structure.

Previously,[1] osmotic studies of the lecithin–benzene system at 25° showed that small micelles were present below a concentration of 0·73 g. $l.^{-1}$; above this concentration (the critical micelle concentration) aggregation to large micelles occurred. The molecular weight of the large micelles could not be obtained directly, but only by fitting a law of mass-action equation to the experimental results, when one of the constants of the equation could be used to calculate the molecular weight. In this paper the molecular weight of the large micelles has been obtained from diffusion measurements, and the shape of the micelles from viscosity measurements. By comparison of experimental results with those calculated from the properties of model structures, it appears that the micelles have a laminar structure.

Experimental

Materials.—The physical properties of the lecithin and benzene used have been reported.[1]

Apparatus.—The apparatus was based on the Gouy diffusiometer described by Gosting *et al.*[2] and by Saunders.[3] All components were mounted on a 2 m. optical bench which rested on a vibration-free girder. Green light ($\lambda = 5461$ Å) from a mercury vapour lamp was isolated by the appropriate interference filter, and illuminated a horizontal slit 12·5 μ in width. The image of the slit was focused through the diffusion cell on a Kodak P2000 photographic plate.

A new diffusion cell, suitable for use with non-aqueous liquids, was designed for the rapid formation and sharpening of boundaries (Fig. 1). The cell had the general form of a U-tube; the two upright arms were 2 × 2 cm. in area, and were made from a single brass block. Part of the face of channel *B* was milled to allow optically flat ($\lambda/2$) cell windows *C* to be fitted. Gaskets for the cell windows were made of a rubber resistant to benzene, and were well extracted before use. A mask *G* fitted over the cell window on the plate side of the cell. The two 1 × 1 mm. square holes cut in the mask were separated by a vertical distance of 5 mm., and were so placed that the boundary was equidistant between them. Photographs of the interference patterns produced by the square holes, first with the solution in the cell, and secondly with the boundary present, provided a means of determining fractional *jm*;[3] *jm* is the difference in optical path length between the two liquids in the cell in wavelengths of light. Photographs for determining fractional *jm* were taken with the triangular aperture of *G* masked. The shape of the aperture helps to cut down the intensity of the undeviated slit image and inner fringes of the pattern, which are usually more intense than the outer fringes.

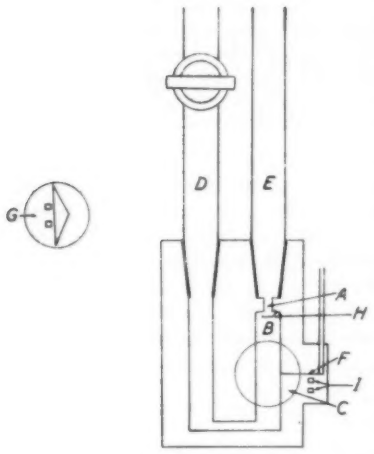
A constriction *A*, diameter 2 mm., length 5 mm., was drilled at the top of *B*. Two glass reservoirs, *D* and *E*, were made to fit into the top of the brass block, and the glass–metal joints were carefully ground and polished until a liquid-tight seal was achieved. The solution-containing reservoir, *D*, had a good quality vacuum tap fused to it. The boundary was sharpened by flow through a 50 μ slit in the cell wall (*F*). The interference pattern from two

[1] Elworthy, *J.*, 1959, 813.
[2] Gosting, Hanson, Kegeles, and Morris, *Rev. Sci. Instr.*, 1949, **20**, 209.
[3] Saunders, *J.*, 1953, 519.

square holes, *I*, cut in the side of the cell, was deflected downwards by an inclined plate of optical glass, and provided a reference trace on the photographic plate from which all distances were measured. The cell was clamped rigidly in a bath fitted with optically flat ($\lambda/2$) windows, and supplied with water from a thermostat regulated at 25° ± 0·05°.

Measurement of Diffusion Coefficients.—The reservoir *D* and U-tube of the cell were filled with solution, the tap on *D* closed, and the solution brought to the middle of the constriction by flow through the slit. The reservoir *E* was inserted, and the cell clamped in position in its bath on the optical bench, and allowed to come to temperature equilibrium. A series of exposures of the reference trace and undeviated slit image were taken. The solvent, or more dilute solution in the case of a semi-differential diffusion, was warmed to a few degrees above 25°, and run slowly into *E* by pipette. The constriction prevented the two liquids from mixing to any extent. Flow through the slit *F* lowered the boundary to slit level, *i.e.*, to the middle of the cell windows. The heights of the liquids in the two reservoirs were equalised, and the tap on reservoir *D* opened. Flow was continued through the slit so that both liquids were flowing out from the cell, and the diffuse region produced by displacement of the boundary downwards from the constriction was swept away. The purpose of the plate *H* (5 × 5 mm.) was to prevent fast-moving liquid emerging from the narrow constriction and impinging directly on the boundary.

FIG. 1.



Flow through the slit was maintained at 1 ml. min.$^{-1}$ for 25 min.; the boundary was finally sharpened by four minutes' flow at 4 ml. min.$^{-1}$. Flow was stopped abruptly by closing a brass clip which constricted the tube carrying the outflow from the cell; diffusion commenced when flow was stopped. Immediately after the start of diffusion the cell was masked so that only the square holes in the cell mask and the reference trace were illuminated. Photographs of the interference patterns were used in the determination of fractional *jm*.

The interference patterns produced by diffusion (the square holes in the cell mask were covered during these exposures) were photographed at timed intervals after the beginning of the experiment; time was measured with an accurate chronometer-watch. Distances on the plate were measured on a Cambridge Universal Measuring Machine to within 0·0002 cm.

Extremely sharp boundaries were produced by this technique, and no correction for Δt[4] (the time taken for an infinitely sharp boundary to reach the state of the existing boundary when diffusion commenced) was necessary, as the diffusion coefficients varied only randomly with time.

Density of Solid Lecithin.—Finely-divided dry lecithin was kept in a stoppered density bottle which was half full of dry acetone for several days, with pumping at intervals to remove air. The density was determined by the usual displacement technique. After the measurement the amount of lecithin used was determined by drying and weighing. Two repeat measurements gave 1·016 and 1·015 g.ml.$^{-1}$.

Viscosity Measurements.—Viscosities relative to benzene were determined in a No. 0 Ostwald capillary viscometer.

Osmotic Pressures.—These were measured as previously described.[1]

RESULTS

The terminology used in describing the diffusion measurements is that of Stigter *et al.*[5] The results of a series of integral diffusion experiments (diffusion into pure solvent) are shown in Table 1.

[4] Longsworth, *J. Amer. Chem. Soc.*, 1947, **69**, 2510.
[5] Stigter, Williams, and Mysels, *J. Phys. Chem.*, 1955, **59**, 330.

TABLE 1. *Integral diffusion coefficients of lecithin in benzene.*

Concn. (g. l.$^{-1}$)	5·00	8·76	15·00	17·45	19·54	20·12	22·83	31·77
$10^6D'$ (cm.^{2} sec.$^{-1}$)	2·27	2·07	$1·79_4$	$1·62_5$	$1·42_1$	$1·58_7$	$1·50_7$	$1·36_9$
jm	6·97	10·60	16·61	19·13	20·92	21·72	24·26	33·15
$\Lambda_{max.}$	0·125	0·089	0·054	0·043	0·033	0·031	0·026	0·008

The patterns obtained in these experiments were characteristic of two-component diffusion. Ct, the ratio of the observed to the theoretical displacement of a fringe above the undeviated slit image, was not constant, but increased as the fringe number decreased. (The outermost fringe in the pattern was numbered zero.) For two-component diffusion the Gaussian distribution curve suffers kurtosis, and the results were best expressed by a weight average diffusion coefficient D', which was calculated by Akeley and Gosting's method.[6] D' was obtained by examining the relative fringe deviation of the patterns; maximum values of the relative fringe deviation, $\Lambda_{max.}$ are shown in Table 1.

Semi-differential diffusion experiments (diffusion from a concentrated into a dilute solution) gave patterns which fitted the theory for single-solute diffusion.

TABLE 2. *Semi-differential diffusion coefficients of lecithin in benzene.*

$\bar{C}$	6·00	15·00	25·00	8·50	12·50	17·78	25·00	32·77
ΔC	10·00	10·00	10·00	15·00	15·00	15·00	15·00	15·00
10^6Da (cm.^{2} sec.$^{-1}$)	1·269	1·281	1·284	1·268	1·272	1·282	1·285	1·294
jm	10·39	10·17	10·18	14·35	14·30	14·15	14·18	14·10

$\bar{C}$ = mean concentration of the two solutions used in an experiment in g. l.$^{-1}$. ΔC = concentration difference between the two solutions in g. l.$^{-1}$.

TABLE 3. *Viscosities of solutions of lecithin in benzene.*

$10^3\phi_1$	$10^3\phi_2$	$\eta_{sp.}$	Correction to $\eta_{sp.}$	ν
0·72	—	0·004	—	6
0·91	1·85	0·010	−0·005	2·7
0·96	4·57	0·021	−0·005	3·5
1·01	10·03	0·048	−0·006	4·2
1·02	12·91	0·066	−0·006	$4·6_5$
1·04	17·37	0·090	−0·006	5·4
1·04	19·83	0·118	−0·006	$5·6_8$
1·05	26·24	0·170	−0·006	$6·2_5$

$\eta_{sp.}$ = observed specific viscosity. $\nu = \eta_{sp.}$ (corrected) ϕ_2^{-1}. A plot of ν against ϕ_2 gave a straight line with an intercept at $\phi_2 = 0$ of $2·7_8$.

Ct was constant, and the height-area average diffusion coefficient, Da, was calculated from Longworth's equation:[4]

$$Da = (b^2\, jm^2\lambda^2)/(4\pi Ct^2 \,.\, t) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where b is the optical distance from the centre of the cell to the photographic plate in cm., λ is the wavelength of the light in cm., and t is the time in seconds at which the photograph was taken.

All patterns were formed above the undeviated slit image, since the refractive indices of lecithin solutions were less than those of solvent or more dilute solutions.

The viscosity results are shown in Table 3. There was a small relative viscosity at 0·73 g. l.$^{-1}$, the critical micelle concentration, where the solute was present mainly as small micelles. To obtain the relative viscosity due to the large micelles, the results were corrected by subtracting the relative viscosity due to the small micelles (obtained from a knowledge of the relative viscosity at 0·73 g. l.$^{-1}$, and the concentrations of small micelles present in the solution) from the total observed relative viscosity. The volume fraction of the small micelles, ϕ_1, and the large micelles, ϕ_2, were calculated from the concentrations of the two species in a solution, which were obtained from the mass-action equation.[1]

To check that the mass-action equation held at concentrations greater than 10 g. l.$^{-1}$, additional osmotic pressure measurements were made (Table 4). There was reasonable agreement between the observed osmotic pressures and those calculated from the mass-action equation.

[6] Akeley and Gosting, *J. Amer. Chem. Soc.*, 1953, **75**, 5685.

TABLE 4. *Extension of osmotic pressure measurements.*

Concn. (g. l.$^{-1}$)	10·31	15·21	25·04	30·02
$10^2\pi_{obs.}$ (atm.)	1·18	1·47	1·81	2·08
$10^2\pi_{calc.}$ (atm.)	1·18	1·41	1·85	2·07

DISCUSSION

The weight-average diffusion coefficient, D', obtained from integral diffusion measurements, decreases as concentration increases (Table 1). This is expected as the concentration of small micelles, C_1, increases little above the critical micelle concentration, while the concentration of large micelles, C_2, increases rapidly (see Table 5). At high concentration C_2 is twenty to thirty times larger than C_1, and values of D' approach those for the diffusion of large micelles alone. As concentration decreases, the amounts of large and small micelles become more equal, and D' increases, as the diffusion coefficient of the small micelles has more effect on the averaging process which produces D'. Also, as concentration decreases, $\Lambda_{max.}$ becomes larger, indicating a larger deviation from a normal Gaussian distribution curve.

The concentration region below 5 g. l.$^{-1}$ could not be explored with the present apparatus, as there was insufficient refractive index difference between the solvent and the solutions to give a reasonable value of jm. For this reason the diffusion coefficient of the small micelles could not be measured directly, but below 20 g. l.$^{-1}$ a plot of $1/D'$ against concentration gave a straight line which could be extrapolated to $D' = 2{\cdot}67 \times 10^{-6}$ cm.^{2} sec.$^{-1}$ at the critical micelle concentration, where the solution consisted almost entirely of small micelles. This value was taken as the diffusion coefficient of the small micelles.

The mass-action equation [1] was used to calculate C_1 and C_2 in a solution of total concentration $C_T = C_1 + C_2$, and from a knowledge of the refractive index increment per unit concentration of the large micelles, α (obtained from the experimental values of jm), D' was calculated from

$$D' = \alpha D_2 + (1 - \alpha)D_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where D_2 was the diffusion coefficient of the large micelles, and D_1 was the diffusion coefficient of the small micelles.

TABLE 5. *Comparison of calculated and observed diffusion coefficients for the integral diffusion of lecithin in benzene.*

C_T	5·00	8·76	15·00	17·45	19·54	20·12	22·83	31·77
C_1	0·97	1·00	1·04	1·05	1·05	1·06	1·06	1·09
C_2	4·03	7·75	13·96	16·39	18·49	19·06	21·77	30·68
$10^6D'_{obs.}$ (cm.^{2} sec.$^{-1}$)	2·3	2·1	1·8	1·6	1·4	1·6	1·5	1·4
$10^6D'_{calc.}$ (cm.^{2} sec.$^{-1}$)	2·0	1·8	1·6	1·6	1·5	1·5	1·5	1·4

There is general agreement between the observed and calculated diffusion coefficients. Large errors occurring in the graphical integrations used in finding $D'_{obs.}$ would account for some of the discrepancies. The agreement confirms the general applicability of the mass-action equation to this system.

The two sets of semi-differential diffusion coefficients (Table 2) at $C = 10{\cdot}00$ and 15·00 g. l.$^{-1}$, show little variation of diffusion coefficient with ΔC, as would be expected in non-polar solvent where charge effects should be almost absent. The pairs of solutions used in each experiment contain almost the same concentrations of small micelles, a consequence of the mass-action law; they differ mainly in their concentrations of large micelles, which is the species diffusing. A plot of Da against concentration yields a straight line, giving $Da = 1{\cdot}264 \times 10^{-6}$ cm.^{2} sec.$^{-1}$ at $C = 0$. This value is taken as the diffusion coefficient of the large micelles.

Size and Shape of the Micelles.—The value of ν when $\phi_2 = 0$ from the viscosity experiments was $2{\cdot}7_8$. A system obeying the postulates on which Einstein's [7] relationship is

[7] Einstein, *Ann. Physik*, 1906, **19**, 289; 1911, **34**, 591.

based would give $\nu = 2{\cdot}5$ when $\phi_2 = 0$. Higher values of ν than 2·5 are attributed either to asymmetry or to solvation of the particles. The large micelles being treated as ellipsoids, and it being assumed that the divergence of ν from 2·5 is due to asymmetry, Mehl, Oncley, and Simha's [8] tables give values for the axial ratios a/b of 1·79 (prolate) or b/a of 1·88 (oblate). These axial ratios can be used to find the ratio of the frictional coefficient of the ellipsoid to that of a sphere of the same molecular weight $(f/f_0)[f/f_0 = 1{\cdot}030$ (prolate) and 1·035 (oblate)].[9]

As $f/f_0 = D_0/D$, where D is the diffusion coefficient of the ellipsoid and D_0 is the diffusion coefficient of a sphere of the same molecular weight, values of D_0 can be calculated from the experimental values of D. For a prolate ellipsoid $D_0 = 1{\cdot}302 \times 10^{-6}$ cm.^{2} sec.$^{-1}$, and for an oblate $D_0 = 1{\cdot}308 \times 10^{-6}$ cm.^{2} sec.$^{-1}$. The molecular weights are 55,200 and 54,400 respectively, calculated from the Stokes–Einstein relationship, the viscosity of benzene being taken as 0·006028 poise.[10]

FIG. 2.

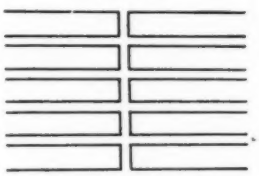
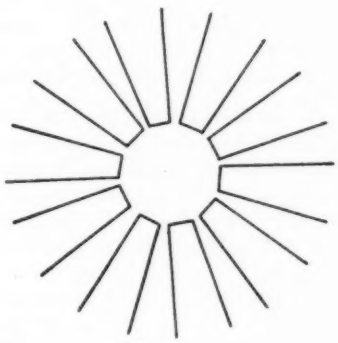


FIG. 3.



The data for the small micelles are not so exact as for the large ones. Only an approximate value of ν can be assigned, owing to the small observed relative viscosity. ν is taken from the result at 0·73 g. l.$^{-1}$ and is approximately 6. A similar procedure to that described above being used, $a/b = 5{\cdot}1$ (prolate), $b/a = 6{\cdot}9$ (oblate), $f/f_0 = 1{\cdot}26$ (prolate), $f/f_0 = 1{\cdot}32$ (oblate), $D_0 = 3{\cdot}4 \times 10^{-6}$ (prolate), and $D_0 = 3{\cdot}5 \times 10^{-6}$ cm.^{2} sec.$^{-1}$ (oblate). The molecular weights were 3100 (prolate) and 2800 (oblate).

Comparison with Model Structures.—It is probable that the polar head groups of the large micelles are turned inwards remote from the benzene, and the hydrocarbon chains of the fatty acids protrude outwards. There are two general possibilities for arrangement of monomers in the micelle. First, as a laminar micelle in which the head groups are arranged as in a sandwich (Fig. 2). Secondly, as a spherical micelle where the head groups are arranged to cover the surface of a sphere (Fig. 3). From a molecular model the overall length of the monomer is 35 Å with fully extended hydrocarbon chains, and the area of the polar head group is 50 Å^2. The length of the monomer is based on the average fatty acid composition of lecithin.

The following calculation shows the spherical arrangement to be unlikely. A micelle containing seventy monomers being taken, arranged as in Fig. 3, it is possible to calculate the radius of the " hole " in the micelle interior. The total radius of the micelle can then be calculated (52 Å) and hence the diffusion coefficient ($7{\cdot}0 \times 10^{-7}$ cm.^{2} sec.$^{-1}$); this is roughly half the observed diffusion coefficient.

[8] Mehl, Oncley, and Simha, *Science*, 1940, **92**, 132.
[9] Svedberg and Pederson, " The Ultracentrifuge," Clarendon Press, Oxford, 1940, p. 41.
[10] Weissberger and Proskauer, " Organic Solvents," Interscience, New York, 1955, p. 72.

XUM

Calculations of the properties of the following models have been made, based on the laminar arrangement and allowance of a 2 Å gap between the two halves of the sandwich: (*a*) Prolate and oblate ellipsoids with a molecular weight of 57,000 (molecular weight from osmotic-pressure measurements). (*b*) Prolate ellipsoids with molecular weight of 55,200 (molecular weight based on diffusion and viscosity data). (*c*) Oblate ellipsoid with a molecular weight of 54,400 (molecular weight based on diffusion and viscosity data). The results of the calculations, as well as the experimental data, are shown in Table 6.

TABLE 6. *Comparison of results from experiment and from models.*

	Experimental		Osmotic		Diffusion–viscosity	
	Prolate	Oblate	Prolate	Oblate	Prolate	Oblate
M	55,200	54,400	57,000		55,200	54,400
n	70·4	69·4	72·7		70·4	69·4
10^6D (cm.^{2} sec.$^{-1}$)	1·264	1·264	1·269	1·219	1·282	1·229
10^6D_0 (cm.^{2} sec.$^{-1}$)	1·302	1·308	1·288		1·302	1·308
f/f_0	1·030	1·035	1·015	1·057	1·016	1·064
ν	2·78		2·63	2·97	2·64	3·04
a/b or b/a	1·79	1·88	1·50	2·24	1·52	2·35
$10^{-6}\beta$	2·15		2·12	2·12	2·12	2·12

M = molecular weight; n = number of monomers in micelle; for β see text.

All figures calculated from models have a moderate agreement with experimental data, indicating that the laminar arrangement of monomers is likely. In general, diffusion coefficients calculated for oblate models diverge rather more from the experimental values than those calculated for prolate models. No absolute choice between the prolate and oblate form can be made owing to the divergence of the actual micelle from perfect ellipsoidal shape, and to the combined errors of the experimental results.

β is a quantity defined by Scheraga and Mandelkern [11] and should depend only on the axial ratio of the ellipsoid. For an increase of b/a from 1 to 300 for oblate ellipsoids, β increases from $2{\cdot}12 \times 10^6$ to $2{\cdot}15 \times 10^6$ and for a prolate ellipsoid variation of a/b from 1 to 300 causes β to increase from $2{\cdot}12 \times 10^6$ to $3{\cdot}60 \times 10^6$. In the present case the choice between oblate and prolate ellipsoids cannot be made as β is insensitive at small axial ratios; it is noteworthy that $\beta = 2{\cdot}13 \times 10^6$ (prolate) and $2{\cdot}12 \times 10^6$ (oblate) for axial ratios of 2 : 1. The value of β calculated from the experimental results is thus in the correct region.

The agreement between the molecular weight from osmotic pressure measurements and that from diffusion–viscosity experiments is good, the molecular weight from the latter methods being lower. If the micelles were much solvated it would be expected that the diffusion–viscosity molecular weight would be larger than that obtained from osmotic pressure, owing to the solvating molecules' travelling with the micelle, and affecting the diffusion coefficient to a large extent.

Consideration of models of the small micelles is based on osmotic data alone, owing to the uncertainties in the determination of the diffusion coefficient and ν. The osmotic molecular weight was 3180, corresponding to four monomers (3140). If these micelles have the same structure as the large ones, the overall length will be 72 Å, and the cross-sectional area at the head groups will be 100 Å^2. In this case the small micelles can only approximate to a prolate ellipsoid. The four-monomer model will have a/b of approximately 7, which is in agreement with the experimental value. The molecular weight obtained from diffusion–viscosity data was 3100. The agreement with the osmotic result is perhaps fortuitous.

I thank Dr. L. Saunders for discussions, and Mr. P. C. Barden for making the cell.

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[11] Shiraga and Mandelkern, *J. Amer. Chem. Soc.*, 1953, **75**, 179.

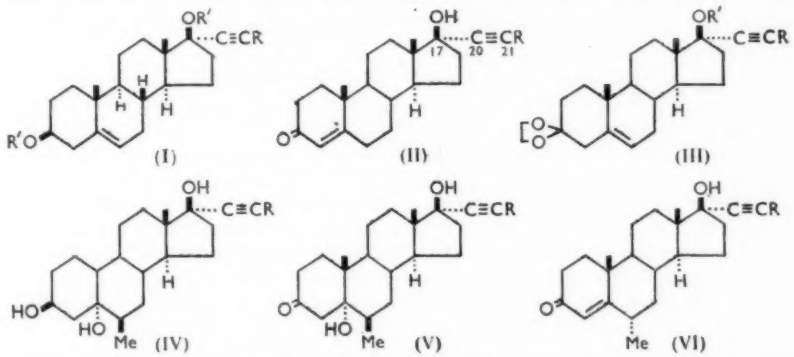
391. *Modified Steroid Hormones. Part XI.* Some Ethisterone Homologues.*

By (Miss) S. P. Barton, D. Burn, G. Cooley, B. Ellis, and V. Petrow.

A method for the conversion of 17α-ethynyl-17β-hydroxy-derivatives of androstane into the $C_{(21)}$-alkyl derivatives is described. Its application to the preparation of the potent progestational agents 21-methyl- † (VI; R = Me) and 21-ethyl-6α-methylethisterone (VI; R = Et) is reported.

Our studies on alkylated steroid hormones [1] are herein extended to some 21-alkyl derivatives of 17α-ethynyl-17β-hydroxyandrost-4-en-3-one (ethisterone) (II; R = H) and its 6α-methyl homologue (VI; R = H).

Initial attempts to prepare the $C_{(21)}$-alkyl derivatives of ethisterone (II; R = H) employed 17α-ethynylandrost-5-ene-3β : 17β-diol (I; R = R′ = H) as starting material. Protection of the two hydroxyl groups was achieved by condensing the diol with 2 : 3-dihydropyran to give the bistetrahydropyranyl ether (I; R = H, R′ = C_5H_9O) as a mixture of isomers which was used directly for alkylation. Conversion of a tertiary hydroxyl group into a tetrahydropyranyl ether has been recorded previously.[2] The bis-ether (I; R = H, R′ = C_5H_9O) with lithamide in liquid ammonia readily gave the 21-metallo-derivative which passed smoothly into a 21-alkyl intermediate on treatment with an alkyl



halide. Regeneration of the 3β- and 17β-hydroxyl groups with ethanolic toluene-*p*-sulphonic acid furnished the 21-alkyl derivatives (I; R = alkyl, R′ = H) which passed into the required 21-alkylethisterones (II; R = alkyl) on Oppenauer oxidation. The 21-methyl, -ethyl, -propyl and -octyl derivatives of 17α-ethynyl-17β-hydroxy-5α-androst-4-en-3-one were obtained in this way. Their biological study [3] revealed that the 21-methyl and the 21-ethyl homologue are superior to the parent steroid (II; R = H) as progestational agents administered by the oral route. The preparation of these compounds was therefore studied further, and an alternative, and in some respects more convenient, reaction sequence developed.

Ethisterone (II; R = H) was converted into its 3 : 3-ethylenedioxy-derivative [4] (III; R = R′ = H) and thence by reaction with 2 : 3-dihydropyran into 3 : 3-ethylenedioxy-17α-ethynyl-17β-(tetrahydro-2-pyranyloxy)androst-5-ene (III; R = H, R′ = C_5H_9O). Alkylation of the ethynyl group by lithamide in liquid ammonia followed by an alkyl

* Part X, *J.*, 1959, 788.

† The nomenclature in the Introductory section is based upon the use of the trivial name "ethisterone" for (II; R = H).

[1] Part VII, *J.*, 1957, 4112.

[2] Elphimoff-Felkin, *Bull. Soc. chim. France*, 1955, 784.

[3] David, Hartley, Millson, and Petrow, *J. Pharm. Pharmacol.*, 1957, **9**, 929.

[4] U.S.P. 2,288,854.

halide, and by removal of the 3- and 17-protecting groups by hot alcoholic oxalic acid, furnished the 21-alkylated ethisterone (II; R = alkyl). In view of the ready availability of the ketone (II; R = H), this route may be preferred as a preparative method.

While this work was in progress, we learnt that 6α-methylethisterone [5] (VI; R = H) is about six times as potent as ethisterone as a progestational agent when tested in the Clauberg assay. Consequently we prepared some 21-alkyl-6α-methylethisterones in the hope that the enhancing effects of 6α- and 21-alkylation on biological activity might prove additive. This was achieved in the following ways.

17α-Prop-1′-ynylandrost-5-ene-3β : 17β-diol (I; R = Me, R′ = H) was oxidised with monoperphthalic acid to the corresponding 5α : 6α-epoxide admixed with some 5β : 6β-epoxide. The former oxide with methylmagnesium iodide furnished 6β-methyl-17α-prop-1′-ynyl-5α-androstane-3β : 5α : 17β-triol (IV; R = Me) which passed into the 3-ketone (V; R = Me) on oxidation with chromium trioxide–pyridine. Treatment of this β-hydroxy-ketone with catalytic amounts of hydrochloric acid in hot ethanol led to dehydration and concomitant epimerisation of the 6β-methyl group (cf. ref. 5) with the formation of 17β-hydroxy-6α-methyl-17α-prop-1′-ynylandrost-4-en-3-one (6α : 21-dimethylethisterone) (VI; R = Me). The higher homologues (VI; R = Et and Pr) were similarly prepared from 17α-but-1′-ynyl- and 17α-pent-1′-ynylandrost-5-ene-3β : 17β-diol, respectively. A second convenient method of obtaining the intermediate triols (IV; R = Me, Et and Pr) involved condensing 17α-ethynyl-6β-methyl-5α-androstane-3β : 5α : 17β-triol [5] (IV; R = H) with 2 : 3-dihydropyran, alkylating the product at $C_{(21)}$ and subsequently removing the protecting groups.

Simple variations of the foregoing routes to 21-alkyl derivatives of 6α-methylethisterone were explored. Thus, 17α-ethynyl-5α : 17β-dihydroxy-6β-methyl-5α-androstan-3-one [5] (V; R = H) was transformed into its 3 : 3-ethylenedioxy-derivative, and the product, after reaction with 2 : 3-dihydropyran, treated with lithamide in liquid ammonia followed by ethyl iodide. Removal of the protecting groups furnished 17α-but-1′-ynyl-5α : 17β-dihydroxy-6β-methyl-5α-androstan-3-one (V; R = Et), from which 21-ethyl-6α-methylethisterone may be obtained (see above). In addition, the immediate precursor (V; R = Pr) of 6α-methyl-21-propylethisterone (VI; R = Pr) was prepared from 3 : 3-ethylenedioxy-17α-pent-1′-ynyl-17β-(tetrahydro-2-pyranyloxy)androst-5-ene (III; R = Pr, R′ = C_5H_9O) by conversion into the corresponding 5α : 6α-epoxide followed by reaction with methylmagnesium iodide and regeneration of the 3- and 17-oxygen functions. Finally, 21-methylation of 17α-ethynyl-6-methylandrost-5-ene-3β : 17β-diol [6] gave 6-methyl-17α-prop-1′-ynylandrost-5-ene-3β : 17β-diol which passed into 6α : 21-dimethylethisterone on Oppenauer oxidation.

Biological study of the foregoing ethisterone homologues revealed that 6α : 21-dimethylethisterone (VI; R = Me) is about twelve times as potent as ethisterone in the Clauberg assay.[3]

Experimental

Rotations were determined in a 1 dm. tube in chloroform unless otherwise stated. Ultraviolet absorption spectra (in ethanol) were kindly determined by Mr. M. T. Davies, B.Sc. B.D.H. alumina (chromatography grade) was used throughout.

17α-Ethynyl-3β : 17β-bis(tetrahydro-2-pyranyloxy)androst-5-ene (I; R = H, R′ = C_5H_9O).—17α-Ethynylandrost-5-ene-3β : 17β-diol (10 g.) in tetrahydrofuran (85 ml.) and 2 : 3-dihydropyran (25 ml.) was treated with phosphorus oxychloride (0·2 ml.). After 3 hr., the mixture was poured into water and the product collected, washed, and crystallised once from aqueous acetone containing 2 drops of pyridine. The *bis-ether* was obtained as a mixture of isomers, needles, m. p. 154—156°, repeated crystallisation of which gave material of m. p. 174°, $[\alpha]_D^{21}$ −120° (*c* 0·6) (Found: C, 77·2; H, 9·8. $C_{31}H_{46}O_4$ requires C, 77·1; H, 9·5%).

17α-Prop-1′-ynylandrost-5-ene-3β : 17β-diol (I; R = Me, R′ = H).—The foregoing compound (4·1 g.) in dry ether (165 ml.) was added during 1 hr. to a stirred solution of ferric nitrate

[5] Part V, *J.*, 1957, 4099.
[6] Part VI, *J.*, 1957, 4105.

(200 mg.) and lithium (0·45 g.) in freshly redistilled liquid ammonia (100 ml.) maintained between −40° and −35°. After a further 2½ hours' stirring, methyl iodide (11 ml.) in dry ether (50 ml.) was added in 30 min. and the stirring continued for a further 3 hr. Ammonium chloride (4 g.) was added, the ammonia allowed to evaporate, and the product, isolated with ether, heated under reflux for 30 min. with toluene-*p*-sulphonic acid (0·6 g.) in ethanol (60 ml.). The solid obtained on the addition of water was purified from aqueous methanol to give 17α-*prop*-1′-*ynyl*-*androst*-5-*ene*-3β : 17β-*diol*, needles, m. p. 179—181°, $[\alpha]_D^{21}$ −121° (*c* 0·98) (Found: C, 76·4; H, 9·7. $C_{22}H_{32}O_2,H_2O$ requires C, 76·3; H, 9·9%). The compound was dried *in vacuo* at 100°, the m. p. remaining unchanged (Found: C, 79·9; H, 9·7. $C_{22}H_{32}O_2$ requires C, 80·4; H, 9·8%). Acetylation in pyridine (18 hr. at 20°) gave the 3β-*monoacetate*, plates (from aqueous ethanol), m. p. 201—202°, $[\alpha]_D^{23}$ −118° (*c* 0·68) (Found: C, 77·6; H, 9·2. $C_{24}H_{34}O_3$ requires C, 77·8; H, 9·25%).

17α-*But*-1′-*ynylandrost*-5-*ene*-3β : 17β-*diol* (I; R = Et, R′ = H), prepared similarly, formed needles (from acetone–hexane), m. p. 78—81°, $[\alpha]_D^{24}$ −121° (*c* 0·83) (Found: C, 81·0; H, 10·2. $C_{23}H_{34}O_2$ requires C, 80·7; H, 9·9%). The 3β-*monoacetate* formed needles (from acetone–hexane), m. p. 134—135°, $[\alpha]_D^{21}$ −116° (*c* 0·67) (Found: C, 77·7; H, 9·3. $C_{25}H_{36}O_3$ requires C, 78·1; H, 9·4%).

17α-*Pent*-1′-*ynylandrost*-5-*ene*-3β : 17β-*diol* (I; R = Pr, R′ = H) formed needles (from acetone–hexane), m. p. 70—71°, $[\alpha]_D^{23}$ −120° (*c* 0·97) (Found: C, 80·5; H, 10·5. $C_{24}H_{36}O_2$ requires C, 80·8; H, 10·2%). The 3β-*monoacetate* formed needles (from ether–light petroleum), m. p. 98—101°, $[\alpha]_D^{20}$ −112° (*c* 1·0) (Found: C, 78·2; H, 9·9. $C_{26}H_{38}O_3$ requires C, 78·3; H, 9·6%).

17α-*Dec*-1′-*ynylandrost*-5-*ene*-3β : 17β-*diol* (I; R = octyl, R′ = H) formed crystals (from acetone–hexane), m. p. 117°, $[\alpha]_D^{21}$ −107° (*c* 0·97) (Found: C, 81·4; H, 10·5. $C_{29}H_{46}O_2$ requires C, 81·6; H, 10·9%).

3 : 3-*Ethylenedioxy*-17α-*ethynylandrost*-5-*en*-17β-*ol* (III; R = R′ = H).—17α-Ethynyl-17β-hydroxyandrost-4-en-3-one (10 g.) and toluene-*p*-sulphonic acid (200 mg.) in benzene (220 ml.) and ethylene glycol (12 ml.) were heated under reflux for 4 hr. in an apparatus fitted with a water-separator. The product crystallised on cooling, and was purified from aqueous pyridine to give the ketal, plates, m. p. 258—259°, $[\alpha]_D^{25}$ −69° (*c* 0·75 in pyridine) (Found: C, 77·35; H, 9·2. Calc. for $C_{22}H_{32}O_3$: C, 77·5; H, 9·05%) (lit.,[4] m. p. 252—254°, $[\alpha]_D$ −90°).

3 : 3-*Ethylenedioxy*-17α-*ethynyl*-17β-(*tetrahydro*-2-*pyranyloxy*)*androst*-5-*ene* (III; R = H, R′ = C_5H_9O).—The foregoing ketal (3·8 g.) in dry tetrahydrofuran (200 ml.) and 2 : 3-dihydropyran (10 ml.) was treated with phosphorus oxychloride (0·08 ml.). After 2½ hr., the mixture was poured into a large volume of dilute aqueous sodium hydrogen carbonate, and the precipitate collected and crystallised once from aqueous acetone to which a few drops of pyridine had been added. The ketal-ether separated as an intimate mixture of blades and needles, m. p. 170—174°, $[\alpha]_D^{23}$ −92° (*c* 0·76 in pyridine) (Found: C, 76·6; H, 8·7. $C_{28}H_{40}O_4$ requires C, 76·3; H, 9·15%), which on fractionation gave *isomer A*, blades, m. p. 184—186°, $[\alpha]_D^{24}$ −107·5° (*c* 1·07 in pyridine) (Found: C, 76·8; H, 8·9%), and a minor proportion of *isomer B*, needles, m. p. 144—145°, $[\alpha]_D^{22}$ −54° (*c*, 0·73 in pyridine) (Found: C, 76·4; H, 8·85%).

17β-*Hydroxy*-17α-*prop*-1′-*ynylandrost*-4-*en*-3-*one* (II; R = Me).—(*a*) A solution of 17α-prop-1′-ynylandrost-5-ene-3β : 17β-diol (1·2 g.) in toluene (100 ml.) and *cyclo*hexanone (40 ml.) was distilled until the distillate became clear. After the addition of aluminium *iso*propoxide (5 g.) in toluene (15 ml.), the mixture was refluxed for 1 hr., cooled, and washed with dilute sulphuric acid, and the solvents were removed in steam. The product, isolated with ether, was purified by passage of its benzene solution through a short column of alumina. Crystallisation from acetone–hexane gave 17β-*hydroxy*-17α-*prop*-1′-*ynylandrost*-4-*en*-3-*one*, needles, m. p. 151—152°, $[\alpha]_D^{25}$ +11° (*c* 0·53 in ethanol), $\lambda_{max.}$ 240 mμ (log ε 4·2) (Found: C, 80·4; H, 9·3. $C_{22}H_{30}O_2$ requires C, 80·9; H, 9·3%).

(*b*) The product (III; R = H, R′ = C_5H_9O) (4 g.; mixed isomers) in tetrahydrofuran (100 ml.) was added dropwise in 1 hr. to a stirred solution of ferric nitrate (0·2 g.) and lithium (1·55 g.) in liquid ammonia (400 ml.) at −40° to −35°. After this had been stirred for a further 2½ hr., a solution of methyl iodide (11 ml.) in ether (50 ml.) was added during 30 min., and the stirring continued for a further 3 hr. Ammonium chloride (5 g.) was added, the ammonia allowed to evaporate, and the product isolated with ether. Its solution in ethanol (200 ml.) was treated with 2% aqueous oxalic acid (100 ml.), and the mixture refluxed for 45 min. Dilution with water gave a solid which crystallised from acetone–hexane in needles, m. p. 151—152°, not depressed in admixture with a sample prepared by method (*a*) above.

17α-*But*-1′-*ynyl*-17β-*hydroxyandrost*-4-*en*-3-*one* (II; R = Et).—(*a*) 17α-But-1′-ynylandrost-5-ene-3β : 17β-diol was oxidised by the Oppenauer method (see previous preparation), and the product chromatographed on alumina. Elution with benzene gave **17α-*but*-1′-*ynyl*-17β-*hydroxyandrost*-4-*en*-3-*one***, plates (from acetone–hexane), m. p. 118—120°, $[\alpha]_D^{23}$ +12° (*c* 0·74 in ethanol), $\lambda_{max.}$ 240·5 mμ (log ε 4·2) (Found: C, 80·6; H, 9·8. $C_{23}H_{32}O_2$ requires C, 81·1; H, 9·5%).

(*b*) The product (III; R = H, R′ = C_5H_9O) was treated with lithamide and then with ethyl iodide under conditions similar to those described above, to give **17α-*but*-1′-*ynyl*-3 : 3-*ethylenedioxy*-17β-(*tetrahydro*-2-*pyranyloxy*)*androst*-5-*ene*** (III; R = Et, R′ = C_5H_9O), needles (from acetone containing a trace of pyridine), m. p. 120—121°, $[\alpha]_D$ −125·5° (*c* 0·97) (Found: C, 76·4; H, 9·4. $C_{30}H_{44}O_4$ required C, 76·9; H, 9·5%). Treatment with hot aqueous-ethanolic oxalic acid, as described above, then gave 17α-but-1′-ynyl-17β-hydroxyandrost-4-en-3-one, plates (from acetone–hexane), m. p. 118—120°, not depressed in admixture with a sample prepared by method (*a*).

17β-*Hydroxy*-17α-*pent*-1′-*ynylandrost*-4-*en*-3-*one* (II; R = Pr),, prepared by (*a*) Oppenauer oxidation of the diol (I; R = Pr, R′ = H) and (*b*) propylation of the product (III; R = H, R′ = C_5H_9O) to give the *derivative* (III; R = Pr, R′ = C_5H_9O), m. p. 104—106°, $[\alpha]_D^{25}$ −136° (*c* 1·07) (Found: C, 77·5; H, 9·55. $C_{31}H_{46}O_4$ requires C, 77·1; H, 9·6%) followed by treatment with aqueous-ethanolic oxalic acid, separated in prisms (from acetone–hexane), m. p. 86—87°, $[\alpha]_D^{23}$ +8° (*c* 0·72 in ethanol), $\lambda_{max.}$ 241 mμ (log ε 4·2) (Found: C, 81·1; H, 9·4. $C_{24}H_{34}O_2$ requires C, 81·3; H, 9·7%).

17α-*Hex*-1′-*ynyl*-17β-*hydroxyandrost*-4-*en*-3-*one* (II; R = Bu), prepared by butylation of the product (III; R = H, R′ = C_5H_9O) followed by removal of the protecting groupings, separated from ether–light petroleum in prisms, m. p. 80—81°, $[\alpha]_D^{21}$ +2° (*c* 1·0 in ethanol), $\lambda_{max.}$ 241 mμ (log ε 4·2) (Found: C, 81·6; H, 10·0. $C_{25}H_{36}O_2$ requires C, 81·5; H, 9·85%). The 2 : 4-***dinitrophenylhydrazone*** formed needles (from chloroform–ethanol), m. p. 156—158° (Found: C, 67·8; H, 7·0; N, 10·2. $C_{31}H_{40}O_5N_4$ requires C, 67·9; H, 7·35; N, 10·2%).

17α-*Dec*-1′-*ynyl*-17β-*hydroxyandrost*-4-*en*-3-*one* (II; R = octyl), prepared by Oppenauer oxidation of the diol (I; R = octyl, R′ = H), separated from acetone–hexane in needles, m. p. 97—99°, $[\alpha]_D^{20}$ +9° (*c* 1·05), $\lambda_{max.}$ 241 mμ (log ε 4·17) (Found: C, 81·6; H, 10·5. $C_{29}H_{44}O_2$ requires C, 82·0; H, 10·4%).

Epoxides derived from **17α-*Prop*-1′-*ynylandrost*-5-*ene*-3β : 17β-*diol***.—The diol (I; R = Me, R′ = H) (10 g.) in tetrahydrofuran (150 ml.) was treated with monoperphthalic acid (10 g.) in ether (120 ml.), and the mixture kept overnight and then poured into 1% aqueous sodium hydroxide (1·5 l.). Most of the ether was removed by aeration, and the solids were collected, washed, and fractionated from aqueous ethanol. The **5α : 6α-*epoxide*** formed needles, m. p. 200—201°, $[\alpha]_D^{24}$ −121° (*c* 0·98) (Found: C, 73·3; H, 9·4. $C_{22}H_{32}O_3,H_2O$ requires C, 72·9; H, 9·45%). The anhydrous ***material*** (Found: C, 76·7; H, 9·4. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·4%) was obtained after drying *in vacuo* at 140°. The **5β : 6β-*epoxide*** separated in plates, m. p. between 180° and 200° depending upon the rate of heating, $[\alpha]_D^{22}$ −58° (*c* 0·78) (Found: C, 72·7; H, 9·0. $C_{22}H_{32}O_3,H_2O$ requires C, 72·9; H, 9·45%). The anhydrous ***material*** (Found: C, 76·9; H, 9·6%) was obtained after drying *in vacuo* at 140°.

3β-*Acetoxy*-5α : 6α-*epoxy*-17α-*prop*-1′-*ynyl*-5α-*androstan*-17β-*ol* separated from chloroform–methanol in prisms, m. p. 245—247°, $[\alpha]_D^{23}$ −110° (*c* 1·0) (Found: C, 74·2; H, 8·9. $C_{24}H_{34}O_4$ requires C, 74·6; H, 8·9%).

3β-*Acetoxy*-5β : 6β-*epoxy*-17α-*prop*-1′-*ynyl*-5α-*androstan*-17β-*ol* formed needles (from aqueous ethanol), m. p. 192—193°, $[\alpha]_D^{22}$ −74° (*c* 1·02) (Found: C, 74·1; H, 8·9%).

5α : 6α-*Epoxy*-3β-*propionoxy*-17α-*prop*-1′-*ynyl*-5α-*androstan*-17β-*ol* crystallised from aqueous methanol in needles, m. p. 206—207°, $[\alpha]_D^{21}$ −104° (*c* 0·9) (Found: C, 74·8; H, 9·1. $C_{25}H_{36}O_4$ requires C, 75·0; H, 9·1%).

5β : 6β-*Epoxy*-3β-*propionoxy*-17α-*prop*-1′-*ynyl*-5α-*androstan*-17β-*ol* separated from aqueous methanol in needles, m. p. 158—160°, $[\alpha]_D^{24}$ −52° (*c* 1·16) (Found: C, 74·8; H, 8·85%).

17α-*But*-1′-*ynyl*-5α : 6α-*epoxy*-5α-*androstane*-3β : 17β-*diol*, obtained by oxidation of the diol (I; R = Et, R′ = H) with monoperphthalic acid in ether–chloroform, separated from acetone–hexane in needles, m. p. 121—123°, $[\alpha]_D^{24}$ −116° (*c* 0·55) (Found: C, 76·6; H, 9·9. $C_{23}H_{34}O_3$ requires C, 77·05; H, 9·6%).

5α : 6α-*Epoxy*-17α-*pent*-1′-*ynyl*-5α-*androstane*-3β : 17β-*diol*, obtained from the diol (I; R = Pr, R′ = H), crystallised from acetone–hexane in needles, m. p. 147—148°, $[\alpha]_D^{22}$ −93° (*c* 1·03) (Found: C, 77·3; H, 10·1. $C_{24}H_{36}O_3$ requires C, 77·4; H, 9·7%).

XUM

6β-*Methyl*-17α-*prop*-1′-*ynyl*-5α-*androstane*-3β : 5α : 17β-*triol* (IV; R = Me).—(*a*) 5α : 6α-Epoxy-3β-propionoxy-17α-prop-1′-ynyl-5α-androstan-17β-ol (5 g.) in benzene (150 ml.) was added to a reagent prepared from magnesium (3·4 g.), methyl iodide (10 ml.), and ether (45 ml.). The mixture was stirred, and some solvent (70 ml.) removed by distillation. After being heated under reflux for 5 hr., the mixture was cooled and acidified with dilute hydrochloric acid, and the organic layer washed neutral. Removal of the solvent gave a solid which was purified from ethyl acetate and then from aqueous ethanol. The *triol* formed needles, m. p. 219—221°, $[\alpha]_D^{21}$ −63° (*c* 0·88) (Found: C, 76·7; H, 9·9. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·1%). The compound frequently separated in a solvated (? hydrated) form and melted (with effervescence) anywhere between 140° and 200°. The 3β-*monoacetate* separated from acetone–hexane in blades, m. p. 185—187°, $[\alpha]_D^{20}$ −57° (*c*, 0·91) (Found: C, 75·1; H, 9·6. $C_{25}H_{38}O_4$ requires C, 74·6; H, 9·5%.

(*b*) Phosphorus oxychloride (0·8 ml.) was added to a stirred suspension of 17α-ethynyl-6β-methyl-5α-androstane-3β : 5α : 17β-triol (12 g.) in dry ether (400 ml.) and 2 : 3-dihydropyran (12 ml.). Dissolution was complete in 30 min. The mixture was set aside overnight, then washed with aqueous sodium hydrogen carbonate and water and dried ($CaCl_2$ for several hours), and the solvent was removed *in vacuo*. The product, a sticky solid, was used without further purification.

Ferric nitrate (0·4 g.) and lithium (2·4 g.) were added to liquid ammonia (400 ml.) at −30° to −40°, and the mixture stirred for 30 min. The foregoing sticky solid (10 g.) in a mixture of tetrahydrofuran (20 ml.) and ether (80 ml.) was added during 45 min., and, after a further 2½ hours' stirring, methyl iodide (21 ml.) in ether (100 ml.) was added during 30 min. Stirring was continued for a further 3 hr., ammonium chloride (20 g.) was added, and the ammonia allowed to evaporate. The product was isolated with ether and heated under reflux for 1 hr. with oxalic acid (10 g.) in methanol (100 ml.) and water (10 ml.). Concentration gave crystals which were purified from aqueous ethanol. The triol formed needles, identical with a specimen prepared by method (*a*) above.

17α-*But*-1′-*ynyl*-6β-*methyl*-5α-*androstane*-3β : 5α : 17β-*triol* (IV; R = Et), prepared from 17α-but-1′-ynyl-5α : 6α-epoxy-5α-androstane-3β : 17β-diol by method (*a*) above, and from 17α-ethynyl-6β-methyl-5α-androstane-3β : 5α : 17β-triol by method (*b*) above, crystallised from acetone–hexane in dimorphic forms, m. p. 110—112° and 168—170°, respectively, $[\alpha]_D$ −53° (*c* 0·72) (Found: C, 73·2; H, 10·1. $C_{24}H_{38}O_3,H_2O$ requires C, 73·4; H, 10·3%). The anhydrous *triol* (Found: C, 77·5; H, 10·0. $C_{24}H_{38}O_3$ requires C, 77·0; H, 10·2%) was obtained after drying for several days *in vacuo* at 50°. The 3β-*monoacetate* crystallised from aqueous methanol in needles, m. p. 191—193°, $[\alpha]_D^{22}$ −63° (*c* 0·91) (Found: C, 74·2; H, 9·4. $C_{26}H_{40}O_4$ requires C, 74·9; H, 9·7%).

6β-*Methyl*-17α-*pent*-1′-*ynyl*-5α-*androstane*-3β : 5α : 17β-*triol* (IV; R = Pr), prepared by methods (*a*) and (*b*) above, crystallised from acetone–hexane in dimorphic forms, m. p. 92—94° and 177—179°, $[\alpha]_D^{22}$ −47° (*c* 0·82) (Found: C, 75·7; H, 10·2. $C_{25}H_{40}O_3,\frac{1}{2}H_2O$ requires C, 75·5; H, 10·4%). Satisfactory analyses for anhydrous material could not be obtained even after drying for several days *in vacuo*. Similar difficulties in analogous series have been reported.[7] The 3β-*monoacetate* crystallised from aqueous methanol in prisms, m. p. 189—191°, $[\alpha]_D$ −56° (*c* 0·79) (Found: C, 75·1; H, 9·6. $C_{27}H_{42}O_4$ requires C, 75·3; H, 9·8%).

5α : 17β-*Hydroxy*-6β-*methyl*-17α-*prop*-1′-*ynyl*-5α-*androstan*-3-*one* (V; R = Me).—The triol (IV; R = Me) (3·4 g.) in pyridine (35 ml.) was added to the complex prepared from chromium trioxide (3 g.) and pyridine (30 ml.), and the mixture kept overnight at room temperature. Benzene (250 ml.) was added, insoluble material removed, and the filtrate washed successively with water, dilute hydrochloric acid, water, dilute aqueous sodium carbonate, and water. Removal of the solvent gave a solid which crystallised from acetone–hexane. The *ketone* formed needles, m. p. 248—250° (decomp.), $[\alpha]_D^{25}$ −45° (*c* 0·82) (Found: C, 76·8; H, 9·5. $C_{23}H_{34}O_3$ requires C, 77·1; H, 9·6%).

17α-*But*-1′-*ynyl*-5α : 17β-*dihydroxy*-6β-*methyl*-5α-*androstan*-3-*one* (V; R = Et), prepared by similar oxidation of the triol (IV; R = Et), crystallised from aqueous methanol in needles, m. p. 225—227° (decomp.), $[\alpha]_D^{18}$ −44·5° (*c* 0·89) (Found: C, 77·6; H, 9·7. $C_{24}H_{36}O_3$ requires C, 77·4; H, 9·7%).

5α : 17β-*Dihydroxy*-6β-*methyl*-17α-*pent*-1′-*ynyl*-5α-*androstan*-3-*one* (V; R = Pr), obtained by oxidation of the triol (V; R = Pr), separated from aqueous methanol in flakes, m. p. 180—182°, $[\alpha]_D^{20}$ −41° (*c* 0·78) (Found: C, 77·1; H, 9·8. $C_{25}H_{38}O_3$ requires C, 77·7; H, 9·9%).

[7] Ushakow and Madaeva, *J. Gen. Chem., U.S.S.R.*, 1939, **9**, 436; Ringold, Batres, and Rosenkranz, *J. Org. Chem.*, 1957, **22**, 99; Campbell, Babcock, and Hogg, *J. Amer. Chem. Soc.*, 1958, **80**, 4717.

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17β-*Hydroxy*-6α-*methyl*-17α-*prop*-1′-*ynylandrost*-4-*en*-3-*one* (VI; R = Me).—A solution of the ketone (V; R = Me) (1·5 g.) in ethanol (45 ml.), to which 4 drops of concentrated hydrochloric acid had been added, was heated under reflux for 1 hr. The mixture was carefully diluted with water and kept overnight at 0° to give a solid which crystallised from aqueous methanol. 17β-*Hydroxy*-6α-*methyl*-17α-*prop*-1′-*ynylandrost*-4-*en*-3-*one* formed plates, m. p. 99—102°, $[\alpha]_D^{24}$ +12° (*c* 1·0), $\lambda_{max.}$ 241 mμ (log ε 4·16) (Found: C, 77·2; H, 9·6. $C_{23}H_{32}O_2,H_2O$ requires C, 77·1; H, 9·6%). The anhydrous *ketone* (Found: C, 80·7; H, 9·4. $C_{23}H_{32}O_2$ requires C, 81·1; H, 9·5%) was obtained after drying over P_2O_5 for 24 hr. at 50°/1 mm. It was hygroscopic.

17α-*But*-1′-*ynyl*-17β-*hydroxy*-6α-*methylandrost*-4-*en*-3-*one* (VI; R = Et), obtained from the ketone (V; R = Et) by the foregoing procedure, crystallised from aqueous methanol in blades, m. p. 74—76°, $[\alpha]_D^{22}$ +17° (*c* 1·02), $\lambda_{max.}$ 241 mμ (log ε 4·16) (Found: C, 77·7; H, 9·95. $C_{24}H_{34}O_2,H_2O$ requires C, 77·35; H, 9·75%). The anhydrous *ketone* (Found: C, 80·8; H, 10·1. $C_{24}H_{34}O_2$ requires C, 81·3; H, 9·7%) was obtained after drying *in vacuo* at 55°.

17β-*Hydroxy*-6α-*methyl*-17α-*pent*-1′-*ynylandrost*-4-*en*-3-*one* (VI; R = Pr), obtained from the ketone (V; R = Pr), crystallised from aqueous methanol in needles, m. p. 83—87°, $[\alpha]_D^{18}$ +10·8° (*c* 0·57), $\lambda_{max.}$ 240·5 mμ (log ε 4·13) (Found: C, 80·4; H, 9·9. $C_{25}H_{36}O_2$ requires C, 81·5; H, 9·85%). There was insufficient material for further purification.

3 : 3-*Ethylenedioxy*-17α-*ethynyl*-6β-*methyl*-5α-*androstane*-5α : 17β-*diol*, obtained by the method used for the preparation of the ketal (III; R = R′ = H), separated from aqueous methanol containing a trace of pyridine, in blades, m. p. 216—217°, $[\alpha]_D^{20}$ −64° (*c* 1·0) (Found: C, 73·9; H, 8·8. $C_{24}H_{36}O_4$ requires C, 74·0; H, 9·3%).

3 : 3-*Ethylenedioxy*-17α-*ethynyl*-6β-*methyl*-17β-(*tetrahydro*-2-*pyranyloxy*)-5α-*androstan*-5α-*ol* crystallised from aqueous acetone containing a trace of pyridine, in plates, m. p. 157—158°, $[\alpha]_D^{21}$ −66° (*c* 0·98) (Found: C, 73·6; H, 9·1. $C_{29}H_{44}O_5$ requires C, 73·7; H, 9·4%). Ethylation in liquid ammonia followed by treatment of the product with hot aqueous ethanolic oxalic acid gave 17α-but-1′-ynyl-5α : 17β-dihydroxy-6β-methyl-5α-androstan-3-one (V; R = Et), identified by mixed m. p. determination and by conversion into 17α-but-1′-ynyl-17β-hydroxy-6α-methyl-5α-androst-4-en-3-one (VI; R = Et).

5α : 17β-*Dihydroxy*-6β-*methyl*-17α-*pent*-1′-*ynyl*-5α-*androstan*-3-*one* (V; R = Pr).—The ketal (III; R = Pr, R′ = C_5H_9O) (2·6 g.) in chloroform (75 ml.) was treated for 18 hr. at 0° with monoperphthalic acid (1·7 g.) in ether (30 ml.). The wax-like product in ether (35 ml.) was added to the reagent prepared from magnesium (2·4 g.), methyl iodide (7 ml.), and ether (50 ml.), and the mixture was stirred at room temperature for 7 hr. and then set aside overnight. The product, isolated with ether as a yellow gum, was heated under reflux ror 1 hr. with oxalic acid (1·4 g.) in ethanol (100 ml.) and water (50 ml.). The product in benzene was chromatographed on alumina to give the ketone, identical with a specimen prepared by an alternative route (above).

17α-*Ethynyl*-6-*methyl*-3β : 17β-*bis*(*tetrahydro*-2-*pyranyloxy*)*androst*-5-*ene* crystallised from acetone containing a trace of pyridine, in needles, m. p. 178—180°, $[\alpha]_D^{20}$ −122° (*c* 0·45) (Found: C, 77·0; H, 9·5. $C_{33}H_{48}O_4$ requires C, 77·4; H, 9·7%).

6-*Methyl*-17α-*prop*-1′-*ynylandrost*-5-*ene*-3β : 17β-*diol*.—The foregoing compound was methylated, to give material which crystallised from acetone in needles, m. p. 161°. Treatment of this substance with hot aqueous ethanolic oxalic acid gave the *diol*, needles (from acetone–hexane), m. p. 111—112° or 135—137°, $[\alpha]_D^{20}$ −103° (*c* 0·6) (Found: C, 81·0; H, 10·1. $C_{22}H_{34}O_2$ requires C, 80·65; H, 10·0%).

17β-*Hydroxy*-6α-*methyl*-17α-*prop*-1′-*ynylandrost*-4-*en*-3-*one* (VI; R = Me) (with Mr. M. Stansfield, A.R.I.C.).—A solution of the foregoing diol (1 g.) in toluene (75 ml.) and *cyclo*hexanone (15 ml.) was distilled until the distillate became clear. Aluminium *iso*propoxide (1 g.) in toluene (15 ml.) was then added, and the mixture heated under reflux for 2 hr. After addition of concentrated aqueous Rochelle salt, the mixture was steam-distilled for several hours, and the product isolated with ether. Crystallisation from aqueous methanol gave plates of 17β-hydroxy-6α-methyl-17α-prop-1′-ynylandrost-4-en-3-one, identical in every respect with a sample prepared by the previously described route.

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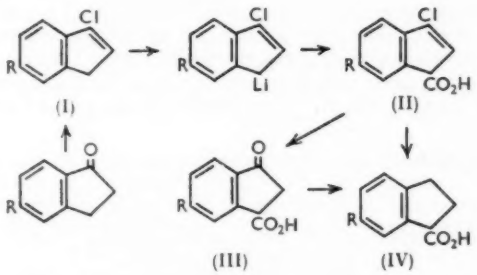
392. *A New Synthetical Route from Indan-1-ones to 3-Oxoindane-1-carboxylic Acids.*

By M. Donbrow.

In a new approach to substitution in the 3-position of the indan-1-ones, 3-chloroindene was converted, *via* its lithium derivative, into 3-chloroindene-1-carboxylic acid. From the latter, 3-oxoindane-1-carboxylic acid and indane-1-carboxylic acid were readily obtained. The same sequence applied to 5-methoxyindan-1-one, gave 6-methoxyindane-1-carboxylic acid in small yield. 3-Bromoindene, prepared by an improved method, failed to give an ethylenic Grignard reagent.

There is no direct method of substituting the 3-position of indan-1-one. Although this position is relatively unreactive in the keto-form, in the enol it corresponds to the active 1-position of the indene nucleus and may be sufficiently activated to permit substitution under enolising conditions. Indan-1-ones and the related 1-oxotetralins and acetophenones are believed to enolise readily under the influence of sodium acetylide and Grignard reagents, since many of the normal ketonic reactions fail.[1-7] Used in equivalent quantity, the reagent would be expected to be destroyed by the enol; a large excess of reagent has no significant effect, for sodium acetylide fails to condense with 5-methoxyindan-1-one [1] or indan-1-one,[2] and the product is mainly unchanged ketone. However, this does not preclude the possibility of a sodium derivative's having been formed at the reactive methylene position (as in indene), for, since the systems lacked a potential reactant for such a derivative, the original ketone would still have been regenerated on acidification.

The problem is simplified by using, in place of the enol, indene derivatives easily formed from and reconverted into indan-1-one, and the reaction was explored through the 3-halogenoindenes.



The lithium derivative of 3-chloroindene [8] was carbonated under conditions which gave a high yield of carboxylic acid from indene (it is not certain whether this is the indene-1- or -3-carboxylic acid). The acidic product from 3-chloroindene contained at least two acids, one of which was 3-chloroindene-1-carboxylic acid (II; R = H); its ultra-violet absorption closely resembled that of indene-1(or 3)-carboxylic acid. Hydrolysis of 3-chloroindene-1-carboxylic acid with hydrochloric acid gave the known 3-oxoindane-1-carboxylic acid [9] (III; R = H) in quantitative yield. Other hydrolytic reagents were

[1] Donbrow, Ph.D. Thesis, Univ. of London, 1956, 54.
[2] Mathieson, Ph.D. Thesis, Univ. of London, 1951, 94.
[3] Hertz, *J. Amer. Chem. Soc.*, 1953, **75**, 73.
[4] Wagner-Jauregg, Arnold, and Hüter, *Ber.*, 1942, **75**, 1293.
[5] Wagner-Jauregg and Hippchen, *ibid.*, 1943, **76**, 694.
[6] Campbell, Campbell, and Eby, *J. Amer. Chem. Soc.*, 1938, **60**, 2882.
[7] Dane, Höss, Bindseil, and Schmitt, *Annalen*, 1937, **532**, 39.
[8] von Braun and Ostermayer, *Ber.*, 1937, **70**, 1006.
[9] Speight, Stevenson, and Thorpe, *J.*, 1924, 2185.

unsatisfactory, 80% sulphuric acid causing partial sulphonation, and alkali causing polymerisation.

Hydrogenation of the 3-chloro-acid yielded indane-1-carboxylic acid [10] (IV; R = H).

5-Methoxyindan-1-one was similarly converted into 3-chloro-6-methoxyindene (I; R = OMe), which, because of its instability, was metallated and carbonated without isolation, yielding an amorphous mixture of acids which was hydrogenated, esterified, and separated by chromatography. A fraction, recognised as a 5- or 6-methoxyindane (light absorption maximum at 283 mμ), was hydrolysed, giving the known 6-methoxyindane-1-carboxylic acid [11] (IV; R = OMe). Traces were also obtained of a high-melting acid (pK_a 4), probably a nuclear-substituted carboxylic acid.

An apparently alternative route to indene-3-carboxylic acid is by carboxylation of the ethylenic Grignard reagent from 3-bromoindene. Jacobi [12] reported success but Porter and Suter [13] have shown that he was using 2-bromoindene. In the present work, 3-bromoindene was prepared by a modification of the method of von Braun and Ostermayer [8] in improved yield. Its ultraviolet absorption is similar to that of 3-chloroindene, except that the low-intensity bands at 279, 285, and 289 mμ are replaced by a single strong band at 287 mμ, ε 2160. There was no reaction between 3-bromoindene and magnesium, however, either under the inverse conditions reported by Jacobi to give a " vigorous " reaction or by use of activated magnesium [14] or the usual variants of the Grignard technique. In view of the increased reactivity observed in 3-chloro-6-methoxyindene, it is possible that an ethylenic Grignard could be formed from 3-bromo-6-methoxyindene.

Experimental

3-Chloroindene-1-carboxylic Acid.—Butyl-lithium (0·04 mole) was prepared by Gilman's method [15] and filtered off under nitrogen. A solution of 3-chloroindene [8] (3·91 g., 0·026 mole; b. p. 57—58°/1 mm.) in dry ether (20 ml.) was added dropwise during 10 min. at $< -10°$. The mixture was kept at room temperature for 10 min. and then carbonated and worked up by the usual method. The aqueous alkaline solution was separated, washed with ether, slightly acidified with dilute sulphuric acid, and extracted with ether. The ether-soluble material, on crystallisation from benzene, gave pale brown needles (1 g.), m. p. 181—182° (decomp.) [Found: C, 61·5; H, 3·6; Cl, 18·4%; equiv., 194 (by rapid direct potentiometric titration in 30% alcohol). $C_{10}H_7O_2Cl$ requires C, 61·7; H, 3·6; Cl, 18·2%; equiv., 195], $\lambda_{max.}$ in water containing 5% of ethanol 225 and 257 mμ (ε 11500 and 4130, respectively). [Indene-1(or 3)-carboxylic acid, prepared from indene and phenyl or *n*-butyl-lithium by the above method, had m. p. 161—162°, $\lambda_{max.}$ in 0·5N-aqueous sulphuric acid 226 and 265 mμ (ε 9600 and 3300, respectively)].

Table 1. *Absorption maxima of some indenes and indan-1-ones (solvent: ethanol).*

Compound	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ) *	ε	Compound	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ) *	ε
Indene	249	9200	279	530	3-Chloro-6-meth-	268	12300	295f	3200
			285f	300	oxyindene			303f	1500
			290f	180	3-Oxoindane-1-	244·5	11300	286	2020
3-Chloroindene ...	253	9550	279	660	carboxylic acid			291	2120
			285f	290	Indan-1-one	244	14400	286	3000
			289f	250				291·5	3100
3-Bromoindene ...	253	10100	297	2160					

* f = flat.

[10] Linnell, Mathieson, and Modi, *J.*, 1953, 3257.
[11] Askam and Linnell, *J.*, 1954, 4691.
[12] Jacobi, *J. prakt. Chem.*, 1931, **129**, 55.
[13] Porter and Suter, *J. Amer. Chem. Soc.*, 1935, **54**, 2022.
[14] Gilman and Kirby, *Rec. Trav. chim.*, 1935, **54**, 577.
[15] Gilman, Beel, Brannen, Bullock, Dunn, and Miller, *ibid.*, 1949, **71**, 1499.

Phenyl-lithium, in place of *n*-butyl-lithium, gave a smaller yield of acids, and the 3-chloroindene-1-carboxylic acid was accompanied by traces of a yellowish-brown amorphous acid, m. p. 195°, sparingly soluble in chloroform and benzene, soluble in ethanol. When phenyl-lithium was used, the main product, on fractionation, gave (*a*) a liquid, b. p. 46°/0·2 mm., and (*b*) traces of diphenyl, b. p. 50°/0·2 mm., m. p. 69°. The main liquid had an absorption maximum at 253 mμ, characteristic of the 3-chloroindene system, and contained chlorine. It decomposed in a few hours at 15° under nitrogen to a green crystalline mass. The tar was removed with boiling benzene and the remainder dissolved in boiling chloroform, from which a tangled skein of white fibres, m. p. 350° (decomp.), axially twisted and birefringent, slowly separated.

3-Oxoindane-1-carboxylic Acid.—3-Chloroindene-1-carboxylic acid (0·3 g.) was refluxed with hydrochloric acid (10 ml.) for 4 hr. The solution was cooled, nearly neutralised, and extracted with ether. The extract gave pale yellow plates (0·27 g.), m. p. 114—116°. Crystallisation from boiling water gave hydrated 3-oxoindane-1-carboxylic acid in plates, m. p. 83·5° (lit.,[9] m. p. 84°). Stored in a vacuum desiccator (H_2SO_4), this effloresced to the anhydrous acid, m. p. 118° (lit.,[9] m. p. 120°) [Found: equiv., 177 (by semimicro-potentiometric titration). Calc. for $C_{10}H_8O_3$: equiv., 176]. Methyl 3-oxoindane-1-carboxylate 2 : 4-dinitrophenylhydrazone was prepared by boiling the free acid with Brady's reagent in methanol for 3 min.; it formed red plates, m. p. 232° (from glacial acetic acid) (Mathieson[16] gives m. p. 232—233°) (Found: C, 55·0; H, 3·7; N, 15·2. Calc. for $C_{17}H_{14}O_6N_4$: C, 55·1; H, 3·8; N, 15·1%).

When 3-chloroindene-1-carboxylic acid was heated for 4 hr. at 80° with 80% sulphuric acid, cooled, and diluted with water, 50% of starting material was deposited, and the remaining product was highly soluble in water and could not be extracted or precipitated. Alkaline hydrolysis gave a dark brown non-ketonic acid, m. p. 200° (decomp.), resistant to purification.

Indane-1-carboxylic acid.—(i) A solution of 3-chloroindene-1-carboxylic acid (0·195 g.) in ethanol (10 ml.) was hydrogenated [catalyst, 5% palladised strontium carbonate (0·6 g.)] to yield a mixture of the acid and ester, which was hydrolysed with 20% sodium hydroxide. Indane-1-carboxylic acid (0·115 g., 71%) was obtained by ether extraction of the acidified solution; it had m. p. 56° (from water containing a trace of dilute hydrochloric acid) (lit.,[10] m. p. 55—56°) [Found: equiv., 162 (by potentiometric titration). Calc. for $C_{10}H_{10}O_2$: equiv., 162]. The *p*-toluidide formed needles, m. p. 162—163° (lit.,[10] m. p. 162—163°) (Found: C, 81·0; H, 6·9; N, 5·5. Calc. for $C_{17}H_{17}ON$: C, 81·3; H, 6·9; N, 5·6%).

(ii) 3-Oxoindane-1-carboxylic acid (0·15 g.) was refluxed for 15 hr. with freshly-prepared zinc amalgam (0·44 g.) and a 1 : 1 mixture of hydrochloric acid and water (1 ml.). The cooled mixture yielded indane-1-carboxylic acid (0·1 g.), m. p. and mixed m. p. 56° (from acidified water) (Found: equiv., 163).

3-Chloro-6-methoxyindene.—This was prepared from phosphorus pentachloride (16·6 g.) and 5-methoxyindan-1-one (12·2 g.) in benzene (150 ml.) by the method used for 3-chloroindene. After removal of the benzene and phosphorus oxychloride at 12 mm., the liquid was fractionated, yielding (*a*) 3-chloro-6-methoxyindene (main fraction), b. p. 115—116°/1—2 mm., (*b*) b. p. 118—140°/1—2 mm. (containing some unchanged 5-methoxyindan-1-one). The fractions solidified and rapidly became tarry, even under nitrogen, and particularly during isolation after attempted recrystallisation from ether. Analytical data were obtained on samples from the first fraction, freshly recrystallised from ether, dried quickly by aspiration with nitrogen and weighed into tared flasks containing ethanol [Found (by hydrolysis with 50% sulphuric acid, partial neutralisation, and potentiometric titration with silver nitrate): Cl, 19·4. Calc. for $C_{10}H_9OCl$: Cl, 19·6%)]. 5-Methoxyindan-1-one was recovered from the hydrolysate. The ultraviolet absorption, determined on ethanol solutions similarly prepared (Table 1), readily distinguished the chloromethoxyindene from 5-methoxyindan-1-one, which has additional characteristic peaks at 287·5 and 294·5 mμ.

Subsequent preparations were conducted under a stream of dry nitrogen, which was led into a series of potash traps, the contents of which were periodically analysed for chloride content. Evolution of hydrogen chloride was complete, and 95% of theory, after 6 hr. After removal of the benzene and by-products under nitrogen, the absence of 5-methoxyindan-1-one was shown spectrophotometrically, and the chlorine content of a sample checked by reduction with sodium in alcohol and argentometric titration.

[16] Mathieson, personal communication.

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6-*Methoxyindane-1-carboxylic Acid*.—Crude 3-chloro-6-methoxyindene (4·51 g., 0·025 mole), prepared as above, was dissolved in 1 : 1 benzene–ether and treated with a solution of *n*-butyl-lithium (0·03 mole) at 15°. The solution was carbonated immediately. The crude *acid* (1·2 g.) yielded pale brown needles (0·2 g.), m. p. 170° (decomp.) (Kofler block), from benzene [Found: Cl, 15·6% (by hydrolysis and potentiometric titration with silver nitrate); equiv., 231 (by hydrolysis). $C_{11}H_9O_3Cl$ requires Cl, 15·8%; equiv., 225].

The crude chloro-acids (0·7 g.) were hydrogenated (5% palladised strontium carbonate) in ethanol, and gave a partially esterified product. The separated ester (0·23 g.) had the ultraviolet absorption of a 5- or 6-methoxyindane ($\lambda_{max.}$ 283 mμ, ε 3200, calc. as $C_{13}H_{16}O_3$). The free acids were esterified with diazomethane, dissolved in the minimum of benzene, and a solution in light petroleum separated on alumina, from which the indane fraction (0·2 g.) was eluted with light petroleum. The combined indane fractions were hydrolysed by boiling 20% hydrochloric acid, giving a near-quantitative yield of 6-methoxyindane-1-carboxylic acid, m. p. 109·5—110° (from boiling water) (Found: C, 68·5; H, 6·4%; equiv., 195. Calc. for $C_{11}H_{12}O_3$: C, 68·7; H, 6·3%; equiv., 192). A mixture with a sample prepared by Dr. V. Askam by Clemmensen reduction of 6-methoxy-3-oxoindane-1-carboxylic acid [11] had the same m. p.

Several amorphous non-volatile fractions were obtained on elution of the alumina column with benzene and benzene–ethanol. On hydrolysis the largest fraction gave an acid, traces of which crystallised from benzene (Found: equiv., approx. 155); it had pK_a 4 (approx.) in 30% ethanol and gave a brown precipitate with ferric chloride solution.

3-*Bromoindene*.—To a stirred suspension of phosphorus pentabromide (46·2 g., 0·106 mole) in benzene (50 ml.) was added a solution of indan-1-one (13·2 g., 0·1 mole) in benzene (25 ml.) followed by benzene (10 ml.), the temperature being kept below 5°. The solution was stirred for 2 hr. at 5° and the bulk of the hydrogen bromide removed at 20°/12 mm. The benzene solution was added to crushed ice (500 g.) and the benzene was separated immediately upon liquefaction, washed with ice-cooled water, 5% sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4). Evaporation and storage over solid carbon dioxide gave pale brown crystals (5·4 g.) of 3-bromoindene. The residual liquid gave two fractions (*a*) b. p. 120—130°/1—2 mm. (indan-1-one) and (*b*) b. p. >140°/1—2 mm. (mainly 3-bromoindene). The yield of 3-bromoindene was 6·8 g. (35%); the yield from the method of von Braun and Ostermayer [8] was 10%. Recrystallised from ether–light petroleum (b. p. 40—60°) 3-bromoindene formed pale yellow prisms (5 g.), m. p. 37° (lit.,[8] m. p. 42°) (Found: C, 55·5; H, 3·6; Br, 40·5. Calc. for C_9H_7Br: C, 55·4; H, 3·6; Br, 41·0%). When refluxed with hydrochloric acid for 6 hr., 3-bromoindene yielded indan-1-one, m. p. and mixed m. p. 42°.

When the reaction mixture was kept for some time before being worked up, the yield of 3-bromoindene was lower and there was also formed a *dibromide*, m. p. 174° (Found: Br, 56·8. $C_9H_7Br_2$ requires Br, 58·0%).

Some of the microanalyses were carried out in the microanalytical laboratory (Mr. Crouch) of the University of London School of Pharmacy. I thank Professor W. H. Linnell for his interest.

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Manresa Road, London, S.W.3. [*Received, September 22nd*, 1958.]

393. *The Effect of Deuteration on Electron Distribution and Energy of Conjugated Molecules. Part I. LCAO–MO Treatment of Toluene.*

By R. Pauncz and E. A. Halevi.

The LCAO–MO treatment of toluene is reconsidered, with inclusion of inductive effects, preliminary to a consideration of the effect of deuteration in the side chain on energy and electron distribution (Part II). It is shown that the two approximations commonly employed yield substantially the same trends. The net charge migration into the ring depends only on the relative electronegativity assumed between the methyl-carbon and the hydrogen atoms, whereas the charge distribution within the ring depends only on the inductive transmission coefficient (ε). Increasing either of these quantities increases the dipole moment, raises the total π-electron energy (destabilisation), but increases the delocalisation energy (stabilisation), so that a more precise definition of "hyperconjugative stabilisation," as generally correlated with hyperconjugative electron release, is called for.

The object of this series of papers is to discuss the effect of deuteration on the properties of conjugated molecules in the ground state. The need for such an investigation arose from consideration of recent work on secondary isotope effects. These effects, first demonstrated in kinetic studies of solvolysis,[1,2] have been interpreted in terms of zero-point energy differences arising from configurational changes between the ground and the transition state. On the other hand it has been shown that polarity differences between isotopic species of the same molecule can be correlated with the slightly different configurations *in the ground state* that arise because of the anharmonicity of the lowest vibrational levels.[3,4] Differences in the acid dissociation constants of methyl- and methylene-deuterated aliphatic acids, which strongly suggest differential inductive effects, are most simply explained on this basis.[5]

In attempting to discuss these effects from a theoretical point of view, it seemed advisable to begin with a study of side-chain deuteration in aromatic systems, since the theoretical methods of LCAO–MO are particularly well adapted to investigations of the properties of conjugated molecules in the ground state and to the study of reactivity, also since experimental work on secondary isotope effects in aromatic substitution is now under way in several laboratories.[6,7]

Since it is expected that the predicted effects will be very small, it is necessary to ascertain that such calculated differences are not inherent in the approximations made in the particular method of calculation; so the present paper is devoted to a reconsideration of the toluene problem including the inductive effect of the methyl group. The specific effects of isotopic substitution in the toluene side chain are taken up in the following paper.

Method of Calculation.—Previous investigations of toluene [8,9] have been related to the general study of hyperconjugation on the basis of the LCAO–MO method. In these treatments the H_3 " pseudo-heteroatom " is assigned a group orbital of p_z symmetry strongly overlapping with the p_z orbital of the methyl-carbon atom which is obtained by resolving the three sp^3 orbitals directed towards the hydrogen atoms into components symmetric and antisymmetric with regard to the plane of the aromatic ring. Factors that have been taken into account differently by various investigators are overlap and the electropositivity

[1] Lewis *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 6306, and later papers.
[2] Shiner *et al.*, *ibid.*, 1953, **75**, 2925 and later papers.
[3] Bell and Coop, *Trans. Faraday Soc.*, 1938, **34**, 1209.
[4] Halevi, *ibid.*, 1958, **54**, 1441.
[5] Halevi and Nussim, *Bull. Res. Council, Israel*, 1956, **5**, *A*, 263; results presented before the 16th Internat. Congr. Pure Appl. Chem., Paris, July, 1957; Halevi, *Tetrahedron*, 1957, **1**, 174.
[6] Swain, Knee, and Kresge, *J. Amer. Chem. Soc.*, 1957, **79**, 505.
[7] Halevi and Ron, unpublished work.
[8] Coulson and Crawford, *J.*, 1953, 2052; Crawford, *ibid.*, p. 2058.
[9] I'Haya, *Bull. Chem. Soc. Japan*, 1955, **28**, 369, 376.

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differences assigned to the various orbitals. The molecular orbitals being written as usual, $\psi_k = \sum x_{kj}\phi_j$; then if overlap between adjacent atoms is included the secular equations are:

$$\sum x_j(H_{ij} - ES_{ij}) = 0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

We use the accepted notation:

$$\left.\begin{aligned} \alpha_i = H_{ii} &= \int \phi_i^* H \phi_i \mathrm{d}v \\ S_{ij} &= \int \phi_i^* \phi_j \, \mathrm{d}v \\ \gamma_{ij} = H_{ij} &= \int \phi_i^* \, H\phi_j \, \mathrm{d}v \end{aligned}\right\} \text{ which are taken as equal to zero for non-adjacent atoms.}$$

The secular determinant has been treated in two ways:

(a) *Wheland's approximation.*[10] γ_{ij} is assumed to be proportional to S_{ij}:

$$\gamma_{ij}/\gamma_o = S_{ij}/S_o = \rho_{ij} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where γ_0 is the resonance integral between adjacent atoms in benzene and S_0 is the corresponding overlap integral (generally taken to be 0·25). When α_0 is written for the standard coulomb integral of a carbon $2p_z$ orbital, a new quantity, β_0, is introduced, defined as:

$$\beta_0 = \gamma_0 - S_0\alpha_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

and electronegativity differences are taken into account by assuming changes in the coulomb integrals, according to:

$$\alpha_i = \alpha_0 + \delta_i\beta_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

One-electron energies being expressed in the form:

$$E = \alpha_0 - \tau\beta_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

the secular equations take the form:

$$x_i(\delta_i + \tau) + \sum_{j \neq i} x_j \rho_{ij} (1 + \tau S_0) = 0 \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Further defining

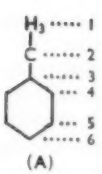
$$k = \tau/(1 + S_0\tau) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

and

$$\xi_i = 1 - S_0\delta_i \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

we can put the secular equations into the particularly convenient form:

$$x_i(\xi_i k + \delta_i) + \sum_{j \neq i} x_j \rho_{ij} = 0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$



(A)

The unknown, k, now appears only in the diagonal elements of the secular determinant.

This is essentially the method employed by Coulson and Crawford[8] in their treatment of toluene. Introducing the notation (A), they used the rounded values $\rho_{12} = 2{\cdot}5$, $\rho_{23} = 0{\cdot}7$, and for all the remaining adjacent orbital pairs assumed $\rho_{ij} = 1$. To account for the greater electropositivity of the methyl group, they assumed the values:

$$\delta_1 = -0{\cdot}5 \quad \delta_2 = -0{\cdot}1 \quad \delta_3 = \delta_4 = \delta_5 = \delta_6 = 0$$

(b) *Mulliken's approximation.*[11] By introducing the quantity, β_{ij}, defined as

$$\beta_{ij} = \gamma_{ij} - \tfrac{1}{2}S_{ij}(\alpha_i + \alpha_j) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3a)$$

and assuming proportionality between β_{ij} and S_{ij}:

$$\beta_{ij}/\beta_0 = S_{ij}/S_0 = \rho_{ij} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2a)$$

[10] Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900.
[11] Mulliken, *J. Chim. phys.*, 1949, **46**, 497.

and retaining (4) and (5), we put the secular equations into the form:

$$x_i(\tau + \delta_i) + \sum_{j \neq i} x_j \rho_{ij}\{1 + S_o(\tau + \tfrac{1}{2}[\delta_i + \delta_j])\} = 0 \quad . \quad . \quad . \quad . \quad (6a)$$

Equation (6*a*) cannot be reduced to a form analogous to (9) unless the coulomb integrals for all atoms are assumed to be equal, in which case the two approximations are identical.

This is essentially the method employed by I'Haya [9] in his treatment of toluene. He used the same values of ρ_{ij} as Coulson and Crawford did, but on the basis of theoretical considerations [12] took:

$$\delta_i = -0{\cdot}3 \quad \delta_2 = -0{\cdot}1 \quad \delta_3 = \cdots \delta_6 = 0$$

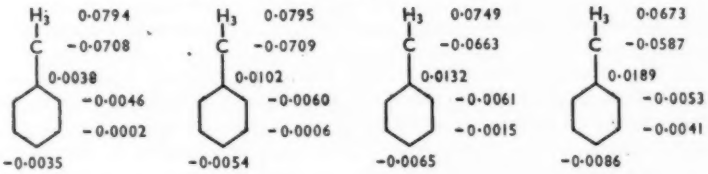
It will be noted that neither of these approximations allows explicitly for the transmission of an inductive effect beyond atom 3. The ability to deal with an inductive effect is essential for our purposes, so we introduce the parameter ε (<1) defined as:

$$\delta_i = \varepsilon\delta_{i-1}$$

which expresses the damping of induced electropositivity through a chain of carbon atoms [13] and prescribes all the values of δ_i once δ_1 and ε have been fixed.

The effect of varying the essential parameters and of using alternative methods of approximation will now be discussed. This will be done separately for the electron distribution and for the energy.

FIG. 1. ($\delta_1 = -0{\cdot}5$.)



	a (Coulson–Crawford)	*b* $\varepsilon = 1/5$	*c* $\varepsilon = 1/4$	*d* $\varepsilon = 1/3$
Dipole moment (D)...	0·276	0·328	0·353	0·415
Net charge migration to ring	0·0085	0·0084	0·0085	0·0085

Electron Distribution. The Rôle of ε *and* δ_1.—Let us first consider the effect on electron distribution of varying the coefficient of inductive transmission, ε. Coulson and Crawford assumed ε to be zero within the ring. Using their method and the value $\delta_1 = -0{\cdot}5$ we have calculated the charge distribution for $\varepsilon = \frac{1}{5}$, $\frac{1}{4}$, and $\frac{1}{3}$. To simplify the calculations the inductive effect was assumed to be carried as far as atom 5 (the *meta*-position) so that $\delta_5 = \delta_6 = 0$. As will appear below, it was necessary to take $\delta_4 \neq 0$, but the further refinement $\delta_5 \neq 0$ is of minor importance.

The results are shown in Fig. 1*a*—*d*. We can see that although the dipole moment increases with increasing ε, this is due entirely to increasing charge separation in the benzene ring as there is no net increase in charge transmitted from the methyl group. Thus if the value of δ_1 is fixed, the correct value of ε depends on what we take to be the correct values for the dipole moment and charge distribution in the ring. On the other hand, if we compare the results of calculations made by using the same inductive transmission but different values of the electropositivities (δ_1) (Fig. 2) we see that, although the dipole moment and net charge migration differ appreciably, the $o : m : p$ net charge ratios

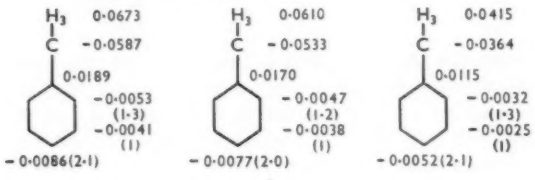
[12] I'Haya, *J. Chem. Phys.*, 1955, **23**, 1165.

[13] (*a*) Branch and Calvin, "The Theory of Organic Chemistry," p. 203, Prentice Hall, New York, 1941; (*b*) Dewar, *J.*, 1949, 463; (*c*) Jaffe, *J. Chem. Phys.*, 1952, **20**, 279, 778; 1953, **21**, 415.

(given in parentheses in Fig. 2) are substantially the same. This means that the correct choice of ε depends solely on what we consider to be a reasonable charge distribution among the ring positions.

The net activation of the *meta*-position in toluene relative to benzene is well established. If this can be taken as an indication of net charge migration to the position in the *ground state* it requires that ε be not equal to zero. (It also requires, as noted above, that the difference of δ_4 from zero be not neglected.) A choice between the alternative values of ε requires a quantitative estimate of ground-state electron distribution which is not directly derivable from the chemical evidence. The ratio of the " partial rate factors " of the *para*- (or *ortho*) to the *meta*-position depends strongly on the electronic requirements of the transition state. Thus for example, the ratio is much less for bromination with a charged bromine cation than for that with a neutral bromine molecule.[14] Even reactions with

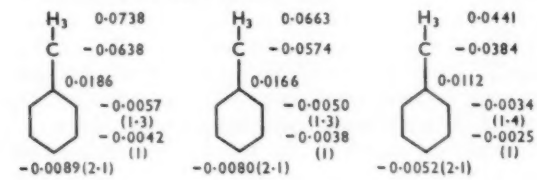
FIG. 2. ($\varepsilon = 1/3$.)



	a	*b*	*c*
δ_1	$-0·5$	$-0·45$	$-0·3$
Dipole moment (D)	0·415	0·372	0·252
Net charge migration to ring	0·0085	0·0077	0·0051

positively charged reagents, which should be better indicators of relative charge distribution, depend considerably on polarisability effects. For example, stabilisation of triphenylmethyl cations by a methyl group is more effective from the *para*- than from the *meta*-positions, but comparatively less so than in nitration or Br^+ bromination.[15] Even here some contribution to stabilisation of the carbonium ion, perhaps the major one, from the *para*-position must come from delocalisation arising from the strong electron demand of the positive centre, and would tend to exaggerate the differences in ground-state distribution in the neutral toluene molecule. The question of the $o : p$ net charge ratio is complicated by steric effects in one direction and possible contributions of polarisability directly through space (direct field effects) in the other.

FIG. 3. ($\varepsilon = 1/3$.)



	a	*b*	*c*
δ_1	$-0·5$	$-0·45$	$-0·3$
Dipole moment (D)	0·444	0·399	0·263
Net charge migration	0·0100	0·0090	0·0057

All in all it seems that any choice of ε between say $\frac{1}{5}$ and $\frac{1}{3}$ would be equally acceptable. In what follows we have arbitrarily adopted a value of $\varepsilon = \frac{1}{3}$, as originally suggested and confirmed on the basis of evidence from other systems.[13]

[14] de la Mare and Harvey, *J.*, 1956, **36**.
[15] Lichtin and Bartlett, *J. Amer. Chem. Soc.*, 1951, **73**, 5530.

Comparison of the Methods.—In order to see to what extent conclusions regarding the electron distribution, dipole moment, and net charge migration depend on the method of calculation adopted, we can compare the results previously obtained with $\varepsilon = \frac{1}{3}$ by Wheland's approximation with the results of calculations based on Mulliken's approximation with the same values of the parameters (Fig. 3). It will be noted that the $o : m : p$ ratio is virtually unaltered in all cases, so that apparently the choice of ε does not depend on the method. Moreover a comparison of the two sets (Figs. 2 and 3) shows that quite good agreement is obtained in the values of the charge distribution, net charge migration, and dipole moment obtained by the two methods for the various values of δ_1.* It appears therefore that any conclusions drawn about the variation of these quantities with the essential parameters would not depend upon the particular method employed.

There finally remains at our disposal a choice of a reasonable value for δ_1, the electropositivity parameter of the H_3 group. It has generally been chosen to yield a value of the dipole moment in the neighbourhood of 0·4 D, the experimental value. Most of the values given above approximate to this. It should be remembered that the total dipole moment of toluene is not necessarily a purely π-electron moment. First, polarisation of the σ-bonds, implicitly taken into consideration in assuming non-zero values of the various δ_i's, is ignored in calculating the total dipole moment. Secondly, corrections for self-consistency have not been made. Thirdly, it is implicitly assumed that the resultant of the *para*-C–H bond moment and the " bond moments " of the two remaining " bonds " for the H_3 pseudo-atom with the group orbital $(a + b + c)$ cancel exactly. Since the C–H bond moments are assumed to be of the order of 0·4 D and to vary with bond type, this too may introduce an error. It appears, therefore, that exact agreement with the experimental value of the dipole moment should not be taken too seriously as a criterion for the proper choice of the parameters, particularly δ_1.

In what follows we have adopted the value −0·45 for δ_1, a value which seems reasonable on the basis of the considerations given above.

Energetic Relations.—General considerations. The essential energetic quantities that are generally calculated directly from a given set of parameters are: The total π-electron energy (E_{mob}); the localised π-electron energy (E_{loc}), calculated with the same parameters but by assuming localised bonds; the delocalisation energy ($E_{\text{del}} = E_{\text{mob}} - E_{\text{loc}}$). The usual measure of the additional stabilisation afforded by the methyl group is the hyperconjugation energy [$E_{\text{hyp}} = E_{\text{del}}^{(\text{toluene})} - E_{\text{del}}^{(\text{benzene})}$]. In order to bring these quantities into relation with thermochemically measured energy differences, additional quantities have had to be taken into consideration. First, differences in the σ-electron energy resulting from the lengthening or shortening of the bonds compared with the standard double and single bonds were accounted for in terms of compression energy (C). Secondly, since even the aliphatic reference molecules are not ideal, in the sense that they undergo some delocalisation, account must also be taken of third-order conjugation energy.

The present investigation is not concerned with choosing the best parameters to fit thermochemical data, but rather with the effect of varying these parameters on the energetic relations. Moreover, compression energies and third-order conjugation energies depend essentially on bond length, and in our calculations bond lengths have been kept constant, so that these quantities also remain constant throughout. (We shall be considering explicitly the effect of variation of the C–H bond length in the following paper but this is irrelevant to the present discussion.)

Even when account is taken of the slight changes in bond lengths that occur when the bond lengths initially assumed are corrected to correspond to the calculated bond orders, the widest variation of bond length encountered in this series of calculations is of the order of 0·002 Å and the corresponding energetic corrections differ by no more than 0·001 β_0 per

* *E.g.*, the decrease of δ_1 from −0·45 to −0·3 decreases the dipole moment and the net charge migration in about the same ratio of 1 to 1·5.

bond, and, summed over the molecule, are negligible in comparison with the other energetic differences. This means that in what follows we can safely restrict ourselves to the variation of the directly calculable quantities, E_{mob} and E_{loc}, and to their difference E_{del}. (E_{hyp} will of course differ from E_{del} by the delocalisation energy of benzene.)

The Rôle of ε *and* δ.—The relevant energetic quantities calculated by using Wheland's approximation are given in Table 1 (in units of β_0). It can be seen that increasing the electropositivity of the H_3 pseudo-atom ($-\delta_1$) leads to a very great reduction in the absolute values of both the total and localised π-electron energies, but to a smaller *increase* in the delocalisation energy. Thus increasing the charge migration to the ring ($-\delta_1$) leads, as one might expect, to an increase in the hyperconjugation energy, but at the same time raises the total π-electron energy to a very much greater extent.

It can also be seen that increasing the value of ε, which is related to charge separation *within* the ring, while holding δ_1 constant, operates in the same direction. However, as Coulson has pointed out,[16] this procedure amounts to altering the average coulomb integral and hence the net attraction of the nuclei for electrons. A comparison of columns 3 ($\delta_1 = -0{\cdot}5$; $\varepsilon = \frac{1}{4}$) and 5 ($\delta_1 = -0{\cdot}45$; $\varepsilon = \frac{1}{3}$), in which the mean coulomb term is approximately the same, shows that the effect of varying ε while keeping the mean coulomb term constant is very much smaller.

TABLE 1.

	$\delta_1 = -0{\cdot}5$ $\delta_2 = -0{\cdot}1$ $\delta_3 = \delta_4 = 0$	$\delta_1 = -0{\cdot}5$		$\delta_1 = -0{\cdot}45$	$\delta_1 = -0{\cdot}3$	
		$\varepsilon = 1/5$	$\varepsilon = 1/4$	$\varepsilon = 1/3$		
$E_{mob} = 8\alpha +$	8·6103	8·5894	8·5584	8·4963	8·5418	8·6816
$E_{loc} = 8\alpha +$	7·5226	7·5003	7·4680	7·4032	7·4492	7·5904
E_{del}	1·0877	1·0891	1·0904	1·0931	1·0926	1·0912
E_{hyp} †	0·0211	0·0224	0·0237	0·0264	0·0260	0·0246
	(1)*	(2)	(3)	(4)	(5)	(6)

* Coulson and Crawford.[8] † $E_{del}^{(benzene)} = 1{\cdot}0666\beta_0$.

Since ε, whatever its true value, is a fixed parameter of the system that will not change with deuteration, the effect of its variation upon the energy will not concern us further. However, hyperconjugative electron-release from alkyl groups to an aromatic ring must arise from an electronegativity difference between the α-carbon atom and the hydrogen atoms bonded to it. The effective electronegativity of the carbon atom can be altered by substitution on it, and that of the hydrogen atoms by isotopic substitution, so that the effect of varying their difference acquires real significance. " Hyperconjugative stabilisation " is generally thought to parallel hyperconjugative electron release. It is now clear that this parallelism depends on just how " hyperconjugative stabilisation " is defined.

In principle the changes in σ-bond energies due to alteration of the electronegativity parameters should also be taken into account, as should have been the σ-dipole moments in the previous discussion.[17] This neglect is particularly unfortunate, since induction presumably operates through the σ-skeleton. However, we see no simple way of dealing with these factors.

TABLE 2.

$\varepsilon = 1/3$	$\delta_1 = -0{\cdot}5$	$-0{\cdot}45$	$-0{\cdot}30$	0
$E_{mob} = 8\alpha +$	8·2207	8·2934	8·5158	8·9665
$E_{loc} = 8\alpha +$	7·1292	7·2022	7·4256	7·8769
E_{del}	1·0915	1·0912	1·0902	1·0896
E_{hyp}	0·0249	0·0245	0·0236	0·0229

Comparison of the Methods.—In Table 2, we have the energetic quantities derived on the basis of Mulliken's approximation, at each of three values of the parameter δ_1 and

[16] Coulson, personal communication.
[17] Craig, personal communication.

fixed value of ε ($\frac{1}{3}$). They are to be compared with columns (4), (5), and (6) of Table 1. The limiting case $\delta_1 = 0$ (in which case the two methods become equivalent) is given too. From the comparison we see that the same trends are obtained with both methods with regard to all the energetic quantities. The values themselves are all somewhat larger when derived from a given value of δ_1 by Wheland's method than by Mulliken's approximation. (The differences, of course, decrease with decreasing δ_1 to zero at $\delta_1 = 0$.) This can be contrasted with what we have seen regarding the charge distribution where the state of affairs was reversed, a greater value of net charge being always predicted on the basis of Mulliken's approximation (other things being equal) than on the basis of Wheland's method.

Excitation Energies.—In view of the common correlation of the electron-donating power of substituents with shifts in the electronic absorption spectra of aromatic molecules, it was of interest to investigate the effect of varying the inductive parameters, particularly δ_1, on the energies of the various transitions. We restricted our considerations to the 2600 Å region. Four transitions yield values in this region. These are * 4 ⟶ 5 and 3 ⟶ 6 both polarised along the long axis, and 4 ⟶ 6 and 3 ⟶ 5 both polarised transversely to this axis.

In Table 3, values of the corresponding transition energies are given (in units of β_0) for both methods, a constant value of ε ($\varepsilon = \frac{1}{3}$) and varying values of δ_1 being used.

TABLE 3.

		Wheland			Mulliken			
Transition	Polarisation	$\delta_1 = -0{\cdot}5$	$-0{\cdot}45$	$-0{\cdot}3$	$-0{\cdot}5$	$-0{\cdot}45$	$-0{\cdot}3$	0
4 ⟶ 5	Long.	2·0774	2·0763	2·0724	2·0539	2·0557	2·0595	2·0619
3 ⟶ 6	,,	2·1383	2·1379	2·1364	2·1334	2·1334	2·1334	2·1333
4 ⟶ 6	Transv.	2·0926	2·0852	2·1020	2·0761	2·0811	2·0938	2·1142
3 ⟶ 5	,,	2·1231	2·1190	2·1068	2·1112	2·1080	2·0996	2·0811

The 2600 Å absorption has been sometimes regarded as corresponding simply to the lowest transition 4 ⟶ 5. We can see that the energy of this transition depends on δ_1, but this dependence is different in the two approximations, approaching the value for $\delta_1 = 0$ in one case from above and in the other from below. Moreover, if the two *transverse* transitions are considered, they are seen to lie quite close together. Their spacing depends on δ_1, both methods predicting that they should cross at a value of $-\delta_1$ somewhat below 0·3. Clearly we must expect very strong interaction between these levels, perhaps strong enough to depress the lower-lying component below the energy of the 4 ⟶ 5 transition. Since transitions 4 ⟶ 5 and 3 ⟶ 6 are not as close together as 4 ⟶ 6 and 3 ⟶ 5 they would be assumed to interact to a smaller extent.

All these considerations tend to render any conclusions based on spectral shifts in this system very doubtful.

General Conclusions.—It should first be noted that the interplay between hyperconjugative and inductive effects, represented here by the parameters δ and ε, are rather more subtle than generally realised. The concept of " hyperconjugative stabilisation " requires careful definition, particularly when it is correlated with " hyperconjugative electron release " as is often done in kinetic discussions.

The introduction of the parameter ε into the calculations was essential in order to obtain a reasonable charge distribution among the ring-carbon atoms. However, since the true ground-state charge distribution in toluene is still in some doubt, the correct value to assume for ε must also remain open. However, it is clear that any choice of ε in the range $\frac{1}{5}$—$\frac{1}{3}$ would not affect any of our conclusions significantly.

In the following paper we shall be concerned with the effects of small changes in some of the molecular parameters on the electron distribution and the various energetic

* The molecular orbitals are numbered in order of increasing energy. This numbering should not be confused with the numbering of the atoms.

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quantities. From the comparison of the results obtained with alternative method of calculation, it appears that the predictions regarding these effects will be essentially independent of the method used.

We are greatly indebted to Professors C. A. Coulson, F.R.S., and D. P. Craig for critically reading the manuscript of this and the following paper, and for many valuable comments.

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HAIFA, ISRAEL. [*Received, October 21st*, 1958.]

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394. *The Effect of Deuteration on Electron Distribution and Energy of Conjugated Molecules. Part II.* LCAO–MO Treatment of* [α-$^2H_3$]-*Toluene.*

By E. A. HALEVI and R. PAUNCZ.

The LCAO–MO treatment of toluene (Part I) is extended to [α-$^2H_3$]toluene, which is assumed to differ from the parent molecule by virtue of a slightly different mean configuration of the methyl group. Increased H_3–C overlap in the deuterated molecule lowers the total π-electron energy, but very slightly decreases the hyperconjugation energy and electron-release to the ring. Increased H · · · H non-bonding interactions have the opposite effect, the changes in the energetic quantities being of the same order of magnitude but the increased electron-release considerably greater. The change in hybridisation of the methyl-carbon atom appears to have a smaller effect in the same direction.

THE object of this paper is to consider possible differences in ground-state properties between [α-$^2H_3$]toluene and the normal toluene molecule on the basis of the LCAO–MO treatment, as discussed in Part I.* Our premise is that dissimilarities between these two molecules can only arise by virtue of a difference in the *mean* configuration of the methyl group. This, in turn, is assumed to result from the anharmonicity of the " zero-point " vibrational levels in the symmetrical stretching and bending modes.

The effect of these configurational differences on the ground-state properties calculated according to the above scheme can be reflected in the following three ways: (1) There is a difference in the overlap integral S_{12},† which depends on both bond length and bond angle. (2) The change in H · · · H distance alters the non-bonding interactions and so affects the effective electropositivity of the H_3 group. (3) The change in bond angle results in a corresponding hybridisation change.

The configurational differences will be discussed first, and their effects on the parameters and through them on the molecular properties will then be taken up.

Configurational Differences.—In order to get the best fit between the rotational constants and molecular dimensions of several isotopic species of the methyl halides, it was necessary to assume that the C–H bond length is 0·005—0·009 Å shorter, and the HCH angle is 12—15′ larger in the trideuterated species than in the normal molecules.[1,2] Since these differences are similar throughout the series CH_3F—CH_3I, they must be relatively insensitive to the size and electronegativity of the atom bonded to the central carbon atom, so that similar configurational differences may be expected in the methyl group of toluene.

Values of the parameters derived from rotational data are not quite the same as the corresponding *mean* values, but it is possible to arrive at an independent estimate of the differences in mean bond length and bond angle on the basis of the harmonic frequencies

* Part I, preceding paper.
† For the definition of this and other symbols, see Part I.

[1] Miller, Aamodt, Dousmanis, Townes, and Kraitchman, *J. Chem. Phys.*, 1952, **20**, 1112.
[2] Andersen, Bak, and Brodersen, *ibid.*, 1956, **24**, 989.

and anharmonicity constants of the symmetrical stretching and bending modes which are treated as if they were completely independent.[3]

By using Hansen and Dennison's data [4] for ethane, as representative o fa methyl group bonded to carbon, the following values are obtained:

$$\bar{r}_{CH} - \bar{r}_{CD} = 0{\cdot}0027 \text{ Å}$$
$$\chi_{HCH} - \chi_{DCD} = 17{\cdot}4' = 0{\cdot}0051 \text{ radian}$$

It is evident from the shape of the Morse curve that the mean length of a C–D bond is less than that of a C–H bond. Since the approximate method employed has been shown in the case of diatomic molecules to yield mean-bond-length differences that are consistently about two-thirds of the accurate value,[3] it is reasonable to take $(\bar{r}_{CH} - \bar{r}_{CD}) = 0{\cdot}004$ Å, in fair agreement with the rotational value. The absolute value of the mean-bond-angle difference calculated is also in reasonable agreement with the spectroscopic results. In order to achieve agreement with experiment in sign as well ($\chi_{DCD} > \chi_{HCH}$), it must be assumed that bringing the three hydrogen atoms closer to each other raises the potential energy less steeply than moving them towards the adjacent carbon atom by a similar change in angle.*

On the basis of these considerations we shall in what follows assume the variation to be in the range:

$$(\bar{r}_{CH} - \bar{r}_{CD}) = 0{\cdot}004\text{—}0{\cdot}009 \text{ Å}$$
$$(\chi_{DCD} - \chi_{HCH}) = 0{\cdot}003_5\text{—}0{\cdot}005 \text{ radian}$$

Change in Overlap.—The numbering scheme of Part I, which begins with the H_3 pseudo-atom, will be used. The overlap integral between the H_3 group orbital possessing $2p_z$ symmetry and the $2p_z$ orbital of the methyl-carbon atom is given by: [5]

$$S_{12} = \sqrt{2}\left(\sin\frac{\chi}{2}\right) S \frac{1}{\sqrt{1-s}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

in which $S \equiv S(1s, 2p\sigma)$; $s \equiv s(1s, 1s)$.

Denoting r_{CH} by r and $r_{H\cdots H}$ by $l(= 2r \sin \chi/2)$ we get for a differential change in S_{12} with bond length and angle:

$$\frac{dS_{12}}{S_{12}} = \left(\frac{1}{S}\frac{dS}{dr} + f \sin\frac{\chi}{2}\right)dr + \frac{\cos\frac{\chi}{2}}{2}\left(\operatorname{cosec}\frac{\chi}{2} + fr\right)d\chi \quad . \quad . \quad . \quad (2)$$

where $f \equiv \dfrac{1}{1-s} \cdot \dfrac{ds}{dl}$.

The 1s–1s and 1s–$2p\sigma$ overlap integrals are standard integrals.[6] They are, in their explicit forms (in atomic units)

$$s = \tfrac{1}{3}\exp(-l)(l^2 - 3l + 3) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$S = \frac{8z^{5/2}}{r^2w^4}\{4z\exp(-r)[wr^2 - 6r - 6] + \exp(-zr)[w^2r^3 + 8z(wr^2 + 3zr + 3)]\} \quad (4)$$

* Professor C. A. Coulson, in a personal communication, has questioned the applicability to toluene of bond-angle changes taken from methyl groups in aliphatic compounds. A better model would certainly be a molecule in which the methyl group is bonded to an unsaturated carbon atom. The available rotational data (see Table IV in Laurie, *J. Chem. Phys.*, 1958, **28**, 706) indicate that here too $\Delta\chi$ is positive and of the same order of magnitude as in the methyl halides, but whether larger ($CH_3{\cdot}C{\equiv}CCl$) or smaller ($CH_3{\cdot}CN$; $CH_3{\cdot}C{\equiv}CH$) is not certain.

[3] Halevi, *Trans. Faraday Soc.*, 1958, **54**, 1441.
[4] Hansen and Dennison, *J. Chem. Phys.*, 1952, **20**, 313.
[5] See, *e.g.*, Lofthus, *J. Amer. Chem. Soc.*, 1957, **79**, 24.
[6] See, *e.g.*, Preuss, "Integraltafeln zur Quantenchemie," Vol. I, Springer, Berlin, 1956.

where z is one-half the Slater effective nuclear charge (for the carbon $2p$ orbital, $z = 1{\cdot}625$, and $w \equiv (z^2 - 1)$.

The expression for dS_{12}/S_{12}, calculated for toluene with the parameters, $\chi = 109° 28'$ (tetrahedral), and $r_{CH} = 1{\cdot}10$ Å, is, with r in Å and χ in radians:

$$\frac{dS_{12}}{S_{12}} = -0{\cdot}50\ dr + 0{\cdot}34\ d\chi \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Substituting the estimated differential changes in mean-bond-length and angle in (5), we note first that the two effects reinforce each other, tending to increase the overlap. The relative change in overlap is found to be in the range:

$$\frac{\Delta S_{12}}{S_{12}} = \frac{S_{CD_3} - S_{CH_3}}{S_{12}} = 0{\cdot}003—0{\cdot}006$$

Taking a rounded value of $S_{12} = 0{\cdot}625$, we obtain:

$$\Delta S_{12} = 0{\cdot}002—0{\cdot}004, \text{ and } \Delta\rho_{12} = \frac{\Delta S_{12}}{S_0} = 0{\cdot}008—0{\cdot}016$$

Effect of Change in Overlap on Energy and Charge Distribution.—On the basis of the above, we may take $\Delta\rho_{12}$ to be of the order of 0·01, and determine to what extent such a change in overlap will affect the energy and charge distribution. In Table 1 are given the differences in the energetic quantities when ρ_{12} is increased or decreased by 0·01 from the reference value of 2·50. In these calculations, carried out according to both Wheland's and Mulliken's approximations, the parameters used are $\varepsilon = 1/3$ and $\delta_1 = -0{\cdot}45$. The absolute values of the energies for $\rho_{12} = 2{\cdot}50$ are given in Tables 1 and 2 respectively of Part I. The energy is in units of β_0.

TABLE 1.

	Wheland		Mulliken	
	$E^{2.51} - E^{2.50}$	$E^{2.50} - E^{2.49}$	$E^{2.51} - E^{2.50}$	$E^{2.50} - E^{2.49}$
ΔE_{mob}	+0·00794	+0·00795	+0·00736	+0·00739
ΔE_{loc}	+0·00810	+0·00812	+0·00753	+0·00755
ΔE_{del} (= ΔE_{hyp})	−0·00016	−0·00017	−0·00017	−0·00016

Both approximations show a strong *increase* of both E_{mob} and E_{loc} with overlap in such a way that the delocalisation energy *decreases* to a very slight extent. This apparently paradoxical decrease in hyperconjugation energy with increasing C≡H_3 overlap is in fact quite reasonable in terms of considerations given by Mulliken, Rieke, and Brown.[7] It should also be noted that this slight decrease is not completely negligible from the point of view of secondary isotope effects. Taking $|\beta_0|$ to be approximately equal to 80 kcal./mole,[8] E_{del} of [α-$^2H_3$]toluene is seen to be some 13 cal./mole lower than that of toluene, which would account for a change of 2—3% in a rate or equilibrium constant at ordinary temperatures. To the extent that a given isotope effect is determined by the difference in *total* π-electron energy, its magnitude would be very much greater.

The energy changes are largely independent not only of the approximation used and the precise value of ρ_{12} assumed in the reference molecules, but also of the inductive parameter, ε. Even assuming the low value of $\varepsilon = 1/5$, we obtain with Wheland's approximation, $\Delta E_{mob} = 0{\cdot}00787$, $\Delta E_{loc} = 0{\cdot}00802$, and $\Delta E_{del} = -0{\cdot}00015$, in good agreement with the values based on $\varepsilon = 1/3$.

The changes in net charge distribution are given in Table 2. Here too, the results are substantially independent of the approximation used and the value of ε, and are insensitive to the precise value of ρ_{12} taken as reference. Although, by virtue of increased overlap,

[7] Mulliken, Rieke, and Brown, *J. Amer. Chem. Soc.*, 1941, **63**, 41.
[8] Coulson and Crawford, *J.*, 1953, 2052.

TABLE 2.

	Wheland			Mulliken	
	$\varepsilon = 1/5$	$\varepsilon = 1/3$		$\varepsilon = 1/3$	
Atom no.	$q^{2.51} - q^{2.50}$	$q^{2.51} - q^{2.50}$	$q^{2.50} - q^{2.49}$	$q^{2.51} - q^{2.50}$	$q^{2.50} - q^{2.49}$
1	−0·00031	−0·00026	−0·00027	−0·00029	−0·00029
2	+0·00024	+0·00020	+0·00021	+0·00021	+0·00022
3	−0·00001	−0·00001	−0·00001	−0·00001	−0·00001
4	+0·00003	+0·00003	+0·00002	+0·00003	+0·00002
5	0·00000	0·00000	0·00000	0·00000	0·00000
6	+0·00002	+0·00002	+0·00002	+0·00002	+0·00003

hyperconjugative electron release from a D_3 pseudoatom is less effective than from H_3, this release effectively goes only as far as the adjacent atom, the changes in charge density on the ring atoms being very small indeed. However, toluene in its ground state represents a system with only weak electron-demand, so that the possibility that overlap differences may be of greater importance in carbonium ions, where electron demand is maximal and hyperconjugation is of the " isovalent " type,[9] cannot be excluded. This question is now under investigation.

Effect of Change in Non-bonding Interaction.—Although the polarity of an isolated CH bond of sp^3 hybridisation is a matter of debate [10] there seems to be general agreement that H_3, acting as a group in CH_3, is more electropositive than the carbon atom to which it is bound. The greater electropositivity of the H_3 group is assumed by Mulliken and his co-workers [11] to be due to non-bonding interaction among the hydrogen atoms. Mulliken gave a first estimate of this difference, and his arguments were made the basis of a more quantitative treatment by I'Haya,[12] who found $\delta_1 = -0{\cdot}3$ for the methylene group and assumed the same value for the methyl group.

Although the expressions for the H_2 and H_3 non-bonding energy are formally identical, the effective Hamiltonian is different in the two cases. The solution of the H_3 problem involves a number of difficulties, but from the form of the Hamiltonian we can infer that in this case electron-release must be greater than from H_2, resulting in a larger value of $-\delta_1$.

Any change in the configuration of the methyl group will change the H · · · H distance, which in turn will affect δ_1. This distance ($l = 2r \sin \chi/2$) will be affected by changing the bond length and bond angle as follows:

$$\mathrm{d}l = 2 \sin \chi/2 \mathrm{d}r + r \cos \chi/2 \mathrm{d}\chi \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

In the range we have assumed for isotopic variation, and with the direction of change as assumed above, the decrease in bond length (r) leads to a decrease in l of the order of:

$$\Delta l_r = (l_{\mathrm{D}} - l_{\mathrm{H}}) = -0{\cdot}011 \pm 0{\cdot}004 \text{ Å}$$

and the increase in angle to an increase in l:

$$\Delta l_\chi = +0{\cdot}0025 \pm 0{\cdot}0005 \text{ Å}$$

the net change being a decrease:

$$\Delta l = -0{\cdot}0085 \pm 0{\cdot}0045 \text{ Å}.$$

Clearly, the H · · · H non-bonding interactions in CD_3 will be greater than in CH_3, and this, on the basis of Mulliken's arguments, would lead to an increase in the absolute value of δ_1, *i.e.*, greater electropositivity of D_3 than of H_3, for which experimental support can be found in the effect of deuteration on the acid dissociation of aliphatic acids.[13]

[9] Muller and Mulliken, *J. Amer. Chem. Soc.*, 1958, **80**, 3489.
[10] See, *e.g.*, Smyth, " Dielectric Behaviour and Structure," McGraw-Hill, New York, 1955, pp. 240—243.
[11] Muller, Pickett, and Mulliken, *J. Amer. Chem. Soc.*, 1954, **76**, 4770.
[12] I'Haya, *J. Chem. Phys.*, 1955, **23**, 1165.
[13] Halevi and Nussim, *Bull. Res. Council Israel*, 1956, **5**, *A*, 263; results presented before 16th Internat. Congr. Pure Appl. Chem., Paris, July 1957.

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Some measure of the change in δ_1 may be had on the basis of I'Haya's treatment. It is found that in the neighbourhood of the normal configuration of the methyl group, decreasing the H $\cdots$ H distance (l) to the extent noted above, results in increasing the absolute value of δ_1 by about 2%. In our scheme of computation, if δ_1 is taken as $-0{\cdot}45$ in toluene it becomes $-0{\cdot}46$ in [α-$^2H_3$]toluene.

Interpolating in the results presented in Table 3 of Part I ($\varepsilon = \frac{1}{3}$; $\delta_1 = -0{\cdot}45$ to $-0{\cdot}50$), we obtain for a change to $\delta_1 = -0{\cdot}46$ the results given in Table 3.

TABLE 3.

	Wheland	Mulliken
ΔE_{mob}	$-0{\cdot}00910$	$-0{\cdot}01454$
ΔE_{loc}	$-0{\cdot}00919$	$-0{\cdot}01461$
ΔE_{del} ($= \Delta E_{\text{hyp}}$)	$+0{\cdot}00009$	$+0{\cdot}00007$

TABLE 4. $(q^{-0{\cdot}46} - q^{-0{\cdot}45})$.

Atom	Wheland	Mulliken	Atom	Wheland	Mulliken
1	$+0{\cdot}00126$	$+0{\cdot}00149$	4	$-0{\cdot}00013$	$-0{\cdot}00015$
2	$-0{\cdot}00109$	$-0{\cdot}00127$	5	$-0{\cdot}00006$	$-0{\cdot}00007$
3	$+0{\cdot}00039$	$+0{\cdot}00039$	6	$-0{\cdot}00017$	$-0{\cdot}00018$

Comparing the results of Tables 1 and 3, we see that the effect on the energetic quantities of methyl deuteration through its effect on electronegativity is opposite in direction and of the same order of magnitude as its effect through the change in overlap.

The effects of variation in δ_1 on charge distribution were discussed extensively an Part I. Since q varies quite linearly with δ_1 in this range, the net charges to be expected in [α-$^2H_3$]-toluene can also be obtained by interpolation. The results for a change from $\delta_1 = -0{\cdot}45$ to $0{\cdot}46$ ($\rho_{12} = 2{\cdot}50$) are given in Table 4.

Comparing Tables 2 and 4 we see that in charge distribution, as in energy, the two effects of deuteration oppose each other. However, with regard to charge distribution, particularly in the ring, the change in electronegativity is about five times as powerful as the change in overlap, and amounts to about 2—3% of the original net charge, which may be an effect of some significance.

Change in Hybridisation.—Another consequence of varying bond angles (but not bond lengths) is a change in the hybridisation parameter, θ, which appears in the expression for the hybrid orbital:

$$t_i = s \cos\theta + p_i \sin\theta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Here t_i is the hybrid orbital and p_i a carbon p-orbital, both directed towards the ith hydrogen (or carbon) atom, and θ is determined by the orthogonality condition ($\int t_i t_k \, d\tau = \delta_{ik}$). Having taken as our reference state a tetrahedral configuration of the methyl group, the hybridisation is pure sp^3, and for each of the four equivalent orbitals $\theta = 60°$.

Now if the DCD angle (χ) is assumed to be slightly greater than tetrahedral, the three orbitals towards the deuterium atoms (t_i^{D}) remain equivalent to each other, but not to the fourth orbital (t^{C}). If account is taken of the dependence of θ on χ and on ξ (the DCC angle) their forms become:

$$t_i^{\text{D}} = s\sqrt{\left(\frac{-\cos\chi}{-\cos\chi+1}\right)} + p\frac{1}{\sqrt{(-\cos\chi+1)}} \quad . \quad . \quad . \quad . \quad (8)$$

$$t^{\text{C}} = s\frac{\cos\xi}{\sqrt{(\cos^2\xi - \cos\chi)}} + p\frac{\sqrt{-\cos\chi}}{\sqrt{(\cos^2\xi - \cos\chi)}}$$

In dealing with hyperconjugative effects, we use the orthonormal transformation

from the three t_i^D (t_a, t_b, t_c) to the following orbitals, the fourth orbital (t^C) remaining unchanged.

$$\left.\begin{aligned} u_1 &= \frac{1}{\sqrt{3}}(t_a + t_b + t_c) \\ u_2 &= \frac{1}{\sqrt{2}}(t_b - t_c) \\ u_3 &= \sqrt{\frac{2}{3}}\left[t_a - \frac{1}{2}(t_b + t_c)\right] \\ u_4 &= t^C \end{aligned}\right\} \quad \ldots\ldots\ldots \quad (9)$$

Of these, the first has σ-type symmetry, and the second and third have π_y and π_z symmetry respectively. Now it follows from (8) and (9) that a symmetric change in HCH angle can affect only u_1 and u_4. In particular, u_3, the orbital entering into conjugation with the ring, remains unaltered.

For the tetrahedral configuration, u_1 and u_4 are given by:

$$\left.\begin{aligned} u_1 &= \frac{\sqrt{3}}{2}s - \frac{1}{2}p_x \\ u_4 &= \frac{1}{2}s + \frac{\sqrt{3}}{2}p_x \end{aligned}\right\} \quad \ldots\ldots\ldots \quad (10)$$

Assuming a maximum angle change of $\Delta\chi = -\Delta\xi = 17'$ (0·005 radian) we obtain:

$$\begin{aligned} u_1' &= 0{\cdot}8706s - 0{\cdot}4922p_x \\ u_4' &= 0{\cdot}4922s + 0{\cdot}8706p_x \end{aligned} \quad \ldots\ldots\ldots \quad (11)$$

The electronegativity of a carbon atom in a hybrid orbital may be assumed to increase linearly with $\cos^2\theta$.[14] Thus in u_1', the carbon atom is more electronegative than in u_1 ($\cos^2\theta' = 0{\cdot}7579$; $\cos^2\theta = 0{\cdot}75$), the change being about 9% of the electronegativity difference between pure sp^3- and sp^2-orbitals. On the other hand, the electronegativity of the carbon atom in the u_4 orbital decreases to the same extent. The net effect is thus a charge migration in the σ-orbitals from the hydrogen atoms in the direction of the ring.

In the tetrahedral configuration there is an electronegativity difference between the σ group-orbital of the hydrogen atoms and u_1, the former being more electropositive.[11] The electronegativity difference between u_4 and the sp^2-orbital of the adjacent ring atom can be split into two parts: (*a*) the intrinsically greater electronegativity of sp^2 than of sp^3; and (*b*) the difference induced, in the same direction, by the hydrogen group. Increasing the HCH angle enhances both effects.

Implicit in our treatment, in which a constant parameter, ε, determines the relative electronegativities of the π-orbitals on adjacent atoms, and does not differentiate between neighbours of the same and different hybridisation of the corresponding σ-orbitals, is that the primary factor is induction, the intrinsic electronegativity difference being assigned relatively minor importance. Having found that increasing the HCH angle increases the $C_{(2)}$–$C_{(3)}$ electronegativity difference by no more than 9% of the *intrinsic* sp^3–sp^2 electronegativity difference, we see that its effect relative to the total difference must be considerably smaller. We must note, moreover, that this effect of angle change appears in the σ-*skeleton*. What we require, and what is in effect represented by the various $(\delta_1 - \delta_k)$'s, are the induced π-electronegativity differences, which result from induction in the σ-skeleton, and may be presumed smaller than the σ-electronegativity differences themselves. This gives us reason to believe that the effect of changing the HCH angle, and hence hybridisation, on $(\delta_2 - \delta_3)$ will be even smaller than its presumed effect on σ-electronegativity differences.

With regard to $(\delta_1 - \delta_2)$, it has been noted that there is no effect of hybridisation change

[14] Moffitt, *Proc. Roy. Soc.*, 1950, *A*, **202**, 534, 548.

on the π-electronegativity difference. Such an effect could only arise indirectly through the change in σ-electronegativity, which we have shown to be small.

All in all, it seems safe to neglect the effect of hybridisation change on electronegativity relative to the primary factor, which we take to be non-bonding interactions. In any event, in passing from toluene to [α-$^2H_3$]toluene the direction of the two effects is the same, and both can be accommodated by an increase in the absolute value of δ_1.

Conclusions.—It appears that of the two configurational differences considered, the shortening of the CH bond in [α-$^2H_3$]toluene is the more important. The increased H_3–C overlap and the increased electropositivity of the H_3 pseudoatom lead to roughly equal and opposite energetic effects. The latter factor is predominant in determining the change in electron distribution, so that electron release to the ring may be sufficiently greater in [α-$^2H_3$]toluene than in toluene for experimental verification.

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395. *Nucleophilic Aromatic Substitution. Kinetics of the Reaction between 1-Chloro-2 : 4-dinitrobenzene and Aromatic Amines in Aqueous Dioxan.*

By J. C. LOCKHART.

The reaction between 1-chloro-2 : 4-dinitrobenzene and *p*-toluidine has been studied in aqueous dioxan as a function of solvent composition. The reaction is faster in the more polar media. There is no simple correlation with dielectric constant but the increase is related to the Grunwald–Winstein factor *Y*,[1] which is a measure of the solvating power of the medium. Addition of salts also increases the rate. Further measurements in pure dioxan with aniline as nucleophil are reported.

MOST nucleophilic aromatic substitutions are bimolecular, except for the S_N1 decomposition of diazonium cations.[2] Two views are held on the mechanism. These differ in whether the intermediate stage is a true transition state [3] or a stable addition complex in equilibrium with the reactants,[4] the distinction being shown by the potential-energy diagram.[5,6] Many data for these reactions, as in the present case, can be interpreted to favour either view.[5-11]

Most workers have obtained second-order kinetics.[2] A more refined analysis of the kinetics of the chlorodinitrobenzene–aliphatic amine reaction by Ross and his co-workers [12,13] has suggested participation of a bimolecular and a termolecular reaction, two amine molecules reacting in the second process. The acceleration observed by Bunnett and Randall [14] when *N*-methylaniline reacts with fluorodinitrobenzene in presence of a base (potassium acetate or sodium hydroxide) is also consistent with a termolecular process.

[1] See Fainberg and Winstein, *J. Amer. Chem. Soc.*, 1956, **78**, 2770.
[2] Bunnett, *Quart. Rev.*, 1938, **12**, 1.
[3] Chapman and Russell-Hill, *J.*, 1956, 1563.
[4] Bunnett and Zahler, *Chem. Revs.*, 1951, **49**, 273.
[5] Bunnett, Garbisch, and Pruitt, *J. Amer. Chem. Soc.*, 1957, **79**, 385.
[6] Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.
[7] Ainscough and Caldin, *J.*, 1956, 2528.
[8] Bunnett and Merritt, *J. Amer. Chem. Soc.*, 1957, **79**, 5967.
[9] Cooper and Hughes, *J.*, 1937, 1183.
[10] Hammond and Parks, *J. Amer. Chem. Soc.*, 1955, **77**, 340.
[11] (*a*) Cortier, Fierens, and Halleux, *Bull. Soc. chim. belges*, 1955, **64**, 709; (*b*) Fierens and Halleux, *ibid.*, p. 717.
[12] (*a*) Ross and Finkelstein, *J. Amer. Chem. Soc.*, 1957, **79**, 6547; (*b*) Ross and Petersen, *ibid.*, 1958, **80**, 2447.
[13] Ross, *ibid.*, 1958, **80**, 5319.
[14] Bunnett and Randall, *J. Amer. Chem. Soc.*, 1958, **80**, 6020.

The authors interpret their data in terms of the intermediate-complex mechanism in which the second step is accelerated by base and the first step becomes rate-determining.

The present example of nucleophilic substitution has been studied as a function of solvent composition. The results confirm the usual second-order kinetics. The reaction between chlorodinitrobenzene and *p*-toluidine was carried out in media containing 0—50% of water by volume. The kinetics in both limiting media were complicated by separation of a second phase. In pure dioxan the separation of amine hydrochloride after 30% of reaction introduced the possibility of heterogeneous catalysis; in 50% dioxan the second phase was a red liquid, probably a saturated solution of dinitrodiphenylamine in dioxan. Reaction of aniline with chlorodinitrobenzene in pure dioxan was also rendered heterogeneous by separation of crystals of amine hydrochloride. Isolation reactions in pure dioxan containing a large excess of amine or chlorodinitrobenzene were studied, and were homogeneous.

Experimental

Materials.—Aniline was fractionally distilled, b. p. 184°, from zinc dust. *p*-Toluidine was recrystallised, m. p. 43°, from light petroleum (b. p. 40—60°). Dioxan was purified by Rische and Milas's method.[15] All salts were " AnalaR."

Kinetic Measurements.—Several samples were made up for each run, in stoppered test tubes, from stock solutions prepared at reaction temperature. Reactions were timed from the addition of chlorodinitrobenzene solution. Samples were analysed for halide by Volhard's method after partition between 15 ml. of benzene, 10 ml. of water, 5 ml. of 4N-nitric acid, and excess of 0·1N-silver nitrate in a separating funnel. The aqueous layer and 2 × 15 ml. washings were titrated with 0·01N-ammonium thiocyanate.

Isolation of Products.—*50% Dioxan.* 40 ml. of reaction solution at infinite time was poured into 100 ml. of distilled water containing 5 ml. of concentrated nitric acid. The red crystals were filtered off, dried, and weighed. The filtrate was neutralised. Its benzene extract on evaporation was combined with the first crystals; yield 94%, m. p. 135·5—136·5° (lit.137 [16]) raised to 136·8—137·5° after recrystallisation from ethanol.

60% Dioxan containing 0·18M-potassium acetate. Yield 97%, m. p. 135·5—136·5°.

Discussion

The reaction in pure dioxan obeyed the kinetic equation

$$dx/dt = k_2(a - 2x)(b - x) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where x is the concentration of *p*-toluidine hydrochloride at time t, a is the initial concentration of amine and b of chlorodinitrobenzene. Plots of log $(a - 2x)/(b - x)$ against

TABLE 1. *Rate constants in pure dioxan.*

p-Toluidine (M)	0·25	0·42	0·25	0·39	5·2	0·025	0·099
$Cl{\cdot}C_6H_3(NO_2)_2$	0·05	0·05	0·10	0·10	0·10	1·05	1·05
Temp.	45°	45°	45°	45°	45°	45°	45°
10^3k_2 (l. mole^{-1} min.$^{-1}$)	1·33	1·35	1·33	1·37	1·36 [h]	1·35 [h]	1·37 [h]
p-Toluidine (M)	0·123	0·248	0·246				
Aniline (M)				0·28	2·75	2·75	5·5
$Cl{\cdot}C_6H_3(NO_2)_2$ (M)	1·05	0·10	0·101	0·05	0·016	0·10	0·10
Temp.	45°	25°	25°	45°	45°	45°	45°
10^3k_2 (l. mole^{-1} min.$^{-1}$)	1·38	0·430	0·408	0·389	0·430 [h]	0·434 [h]	0·628 [h]

[h] Run was homogeneous throughout.

time were linear to at least 60% reaction. Runs with excess of either component gave excellent first-order plots. The results are shown in Table 1. From the corresponding data at 45° and 25°, the Arrhenius activation energy for the chlorodinitrobenzene–*p*-toluidine reaction was estimated at 10·9 ± 0·5 kcal. mole^{-1} (Singh and Peacock [17] report

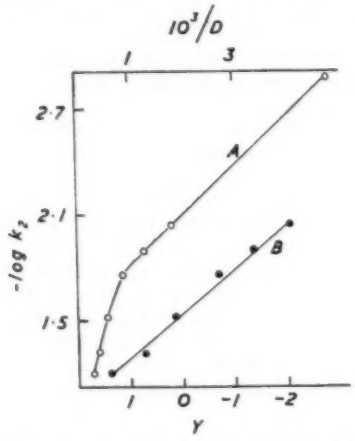
[15] See Weissberger, " Technique of Organic Chemistry. Vol. VII, Organic Solvents," Interscience Publishers Inc., New York, 1955, p. 372.

[16] Kabachnik and Zitser, *J. Gen. Chem. U.S.S.R.*, 1937, **7**, 162.

[17] Singh and Peacock, *J. Phys. Chem.*, 1936, **40**, 669.

10·06 ± 0·3 for reactions of 0·4M-*p*-toluidine and 10·81 ± 0·3 kcal. mole^{-1} for 0·8M-*p*-toluidine in ethanol).

Solvent Effects.—The second-order rate constant for *p*-toluidine in Table 1 shows only a slight increase with increasing amine concentration, even when the solvent is approximately 50% dioxan by volume (5·2M-*p*-toluidine). Similarly when the chlorodinitrobenzene concentration is increased to approximately 25% by volume (1·05M) the rate increase is only a few units per cent. The trend of rate constant with increasing aniline concentration is more definite. When the aniline concentration is increased tenfold to 25% by volume (2·75M), k_2 is increased by 10%; when it is increased to 50% by volume (5·5M) the rate is almost doubled. The latter variation of k_2 may be qualitatively explained by a medium effect since aniline–dioxan solvents should be more polar than the corresponding *p*-toluidine–dioxan or chlorodinitrobenzene–dioxan mixtures.



A, Variation of log k_2 with $1/D$.
B, Variation of log k_2 with Y.

In Table 2 are collected data for reactions in aqueous dioxan solvents at 45°. Eqn. (1) was again obeyed but plots of log $(a - 2x)/(b - x)$ against time showed slight deviation after 60—70% of reaction, possibly owing to the gradually increasing ionic strength of the solution as amine hydrochloride accumulated. The transition state or metastable intermediate would be more polar than the reactants. The reaction rate obviously increases with solvent polarity, as expected for such cases. It has been predicted that for such

TABLE 2. *Variation in k_2 with change of medium at* 45°.

Dioxan (% v/v)	90	90	85	79	79	70	70	60	60	50	50
p-Toluidine (M).....	0·250	0·125	0·250	0·248	0·124	0·124	0·123	0·123	0·122	0·124	0·122
$Cl{\cdot}C_6H_3(NO_2)_2$ (M)	0·05	0·05	0·05	0·05	0·05	0·05	0·05	0·05	0·05	0·05	0·05
10^3k_2 (l. mole^{-1} min.$^{-1}$) ...	0·899	0·875	1·29	1·77	1·74	2·72	2·97	4·71	4·71	6·32 [a]	6·44 [a]

[a] Run heterogeneous after 25% reaction.

a reaction log k should be linear in $1/D$ where D is the dielectric constant of the medium.[18,1] Such relationships are frequently found for reactions in a binary solvent pair in which the dielectric constant can be suitably varied. However, a plot of log k_2 from Table 2 against $1/D$ is a continuous curve (Figure), indicating that the dielectric constant is not an adequate measure of the solvent's rôle in this reaction.

The various properties which contribute to the ability of a solvent to solvate ions can be measured by the quantity Y,[1] termed the " ionising power " of the solvent, which is a function of solute–solvent interaction defined by the relation:

$$\log k = \log k_0 + mY \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

[18] Laidler and Eyring, *Ann. N.Y. Acad. Sci.*, 1940, **39**, 303.

The standard values for Y have been measured in many solvents for the S_N1 solvolysis of *tert.*-butyl chloride at 25°. In 80% ethanol Y is arbitrarily taken as zero and $k = k_0$. The parameter m measures the susceptibility of a reaction to Y relative to that of *tert.*-butyl chloride. The correlation of solvolysis rates by this empirical method [1] is better in many cases than by the method involving dielectric constant. The scope and limitation of eqn. (2) have been investigated.[19-21]

In the current case the Y function has provided a close description of rate variation. A straight-line graph of log k_2 *versus* Y is shown in the Figure. The slope $m = 0{\cdot}250$ and the closeness of fit of eqn. (2) is $\pm 0{\cdot}0472$. An extrapolation of the line to the k_2 value for pure dioxan yields a Y value of $-5{\cdot}34$ for that solvent. Nucleophilic aromatic substitution may thus provide another measure of solvating power in non-hydroxylic media, analogous to Kosower's Z values.[22] A relation of k_2 with Y could be predicted from either the S_N2 or the intermediate-complex viewpoint and this finding does not differentiate between the two.

Salt Effects.—The effect on rate of the salt formed in the reaction (*p*-toluidine hydrochloride which is also an acid), common-ion salt, neutral salts, and potassium acetate was briefly investigated and the results are shown in Table 3. Addition of salt seems to accelerate the reaction slightly, but the results differ slightly for different salts so the effect cannot merely be that of increased ionic strength. Ion pairs and higher aggregates may be important in all the media considered, as the reagent concentrations were high for media of such low polarity. The product, *p*-toluidine hydrochloride, produces roughly a 10% increment on rate when half a mole is present in relation to one mole of chlorodinitrobenzene. Neutral salts in equimolar proportion to chlorodinitrobenzene produce a 6—7% increase, the chloride salt a 10% increase, and potassium acetate a very slight increase. Any specificity of the salt effects is probably accentuated by the low polarity of the medium.

An increase in rate with increase in ionic strength may be predicted for both mechanisms as the transition states will be more polar in each case than the reactants.

TABLE 3. *Salt effects on k_2 in various media at 45°.*

Dioxan (% v/v)	90	90	79	79	70	50	50
p-Toluidine (M)	0·125	0·249	0·124	0·126	0·126	0·124	0·126
$Cl{\cdot}C_6H_3(NO_2)_2$ (M)	0·05	0·05	0·05	0·05	0·05	0·05	0·05
Salt [a]	PTH	PTH	PTH	PTH	PTH	PTH	PTH
(M)	0·0133	0·0133	0·005	0·0133	0·0133	0·0133	0·0269
10^3k_2 (l. mole^{-1} min.$^{-1}$)	0·904	0·902	1·85	1·97	3·13	6·89 [n]	7·27 [n]
Dioxan (% v/v)	60	60	60	60	60		60
p-Toluidine (M)	0·123	0·123	0·123	0·123	0·123		0·123
$Cl{\cdot}C_6H_3(NO_2)_2$ (M)	0·05	0·05	0·05	0·05	0·05		0·05
Salt	KNO_3	$NaClO_4$	KCl	$CH_3{\cdot}CO_2K$	$CH_3{\cdot}CO_2K$		$CH_3{\cdot}CO_2K$
(M)	0·0509	0·0503	0·0509	0·0726	0·185		0·251
10^3k_2 (l. mole^{-1} min.$^{-1}$)	5·09	5·03	5·60	4·76 [b]	5·04 [b]		5·07 [b]

[a] PTH is *p*-toluidine hydrochloride. [b] Values calculated from the kinetic equation, $dx/dt = k(a - x)(b - x)$ because potassium acetate reacts with amine hydrochloride to give free amine and acetic acid, and so only one amine molecule is used up in the reaction. A plot of log $(a - 2x)/(b - x)$ against time curves strongly for the last two runs, although log $(a - x)/(b - x)$ gives a straight line to 80% reaction for the last three runs.

[n] Run heterogeneous after 25% reaction.

The effect of acid (*p*-toluidine hydrochloride) is of the magnitude of a salt effect, and there is no apparent catalysis by the base potassium acetate.

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[19] Wilputte-Steinert and Fierens, *Bull. Soc. chim. belges*, 1955, **64**, 308.
[20] Winstein, Fainberg, and Grunwald, *J. Amer. Chem. Soc.*, 1957, **79**, 4146.
[21] Hudson and Saville, *J.*, 1955, 4114.
[22] Kosower, *J. Amer. Chem. Soc.*, 1958, **80**, 3253, 3261, 3267.

396. *Preparation of Germane. Part I. Reaction between Lithium Aluminium Hydride and Germanium Tetrachloride.*

By E. D. Macklen.

A study of the effects of temperature and of the order of addition of reactants has been made for the reaction between lithium aluminium hydride and germanium tetrachloride in tetrahydrofuran. Higher reaction temperatures favour the production of germane, whereas temperatures below 0° favour side reactions which limit the yield of germane. The decomposition of trichlorogermane and the subsequent reaction of germanium dichloride with lithium aluminium hydride is suggested to explain the low yields of germane. Under the best conditions a 40% yield of monogermane was obtained.

Although monogermane was first produced in 1902 [1] its properties were little known until much later, as the yields and purity of samples were very low. The first successful preparation, by the action of dilute acids on magnesium germanide, was developed by Dennis, Corey, and Moore,[2] who obtained a 22·7% yield of mixed germanes containing 16·8% of monogermane. This method was later improved by Kraus and Carney [3] by replacing the dilute acid by ammonium bromide in liquid ammonia, and a yield of 70% of mixed germanes containing predominantly monogermane was obtained. No new method of preparation was reported until 1947 when Finholt, Bond, Wilzbach, and Schlesinger [4] prepared germane, silane, and stannane by the metathetical reaction between lithium aluminium hydride and the corresponding tetrachlorides in diethyl ether. For germane the reaction can be represented by the equation:

$$LiAlH_4 + GeCl_4 \longrightarrow GeH_4 + LiCl + AlCl_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad 1)$$

Although the preparation was quantitative for silane, the yields of germane (27·7%) and stannane [5] (20·4%) were rather low.

Since the production of litre quantities of germane was ultimately required it was felt that a more detailed study of the reaction between lithium aluminium hydride and germanium tetrachloride might result in a considerable improvement in yield. Details of investigations into the effect of temperature and order of addition of reactants are given here.

Experimental

Apparatus.—The reaction vessel consisted of a 500 ml. three-necked flask fitted with a water-cooled condenser and a cold-finger condenser, a thermometer pocket, a graduated tap funnel with adaptor for inert-gas entry, and a magnetic stirrer. The cold-finger condenser, kept at −80° with solid carbon dioxide–acetone, was connected *via* a preliminary cold trap at −80° to the collection system consisting of four traps in parallel enabling separate fractions to be collected by condensation with liquid nitrogen during reaction. Attached to a manifold common to the four traps were two storage vessels, V_1 and V_2, of volumes approximately 0·5 and 5·0 l., a three-column mercury manometer (one reference column and two measuring columns), and two limbs of volumes approximately 10 ml. and 100 ml. These limbs were used for vapour-pressure measurement and analysis by thermal decomposition respectively.

Materials.—Most of the work was carried out with tetrahydrofuran as solvent, and, except where stated, the following solutions were used.

Lithium aluminium hydride solution. Commercial tetrahydrofuran was dried by refluxing it for several hours with calcium hydride in dry nitrogen, then distilled directly on powdered

[1] Voegelen, *Z. anorg. Chem.*, 1902, **30**, 325.
[2] Dennis, Corey, and Moore, *J. Amer. Chem. Soc.*, 1924, **46**, 657.
[3] Kraus and Carney, *ibid.*, 1934, **56**, 765.
[4] Finholt, Bond, Wilzbach, and Schlesinger, *ibid.*, 1947, **69**, 2692.
[5] The yield of stannane from this reaction has recently been raised to 80—90% by inhibition of SnH_4 decomposition by traces of oxygen; Emeléus and Kettle, *J.*, 1958, 2444.

lithium aluminium hydride. The mixture was refluxed in nitrogen for one day to effect solution and drive off volatile impurity hydrides, then allowed to cool and settle. The solution was siphoned from the residual solid when required. The amount of active lithium aluminium hydride in the solution was determined by hydrolysis and by oxidation with iodine to be 8·0 g. per 100 ml. of solution (2·11M).

Germanium tetrachloride solution. A solution of approximately the same molarity as that of the hydride was prepared by diluting 26 ml. of germanium tetrachloride to 100 ml. with dry tetrahydrofuran (2·28M).

Reactants in dioxan. Dioxan was dried by refluxing it with calcium hydride for several hours. A slurry of 6 g. of powdered lithium aluminium hydride in 75 ml. of dioxan was prepared in the reaction flask. A solution of 13 ml. of germanium tetrachloride diluted to 50 ml. with dioxan was also prepared.

Procedure.—A known volume of one reactant was placed in the flask and hydrogen passed through for 30 min. before the second reactant was added slowly to the flask from the tap funnel. The flask temperature was kept constant. A steady temperature as recorded by the thermometer placed in mercury in the thermometer pocket was maintained before reaction commenced. The hydrogen and the germane evolved passed through the condensers and preliminary cold trap (used to remove entrained solvent) into the first of the four traps cooled with liquid nitrogen. The germane solidified and the hydrogen passed to exhaust. The addition of the second reactant was stopped after a fixed volume of solution had been added. After a further 15 min., during which any germane remaining in the flask was swept by the hydrogen into the collection system, the first liquid-nitrogen trap was closed, the second trap opened, and the addition of the second reactant continued. This was repeated until the four traps contained germane. The collection system was then evacuated of hydrogen and the contents of each trap were evaporated in turn by raising the trap temperature, the gas evolved expanded into one of the two vessels $V_{1,2}$, and the pressure read on the mercury manometer. The volume of gas at room temperature was then calculated and corrected to S.T.P. The germane was then recondensed in a storage trap and the four collection traps were then available for the collection of further fractions of germane. By this procedure the evolution of germane at each stage of the addition of the second reactant could be followed. Excess of the second reactant was added in every case to ensure complete removal of the first reactant. At the end of reactions at low temperatures the flask temperature was slowly raised to the boiling point of the solvent, and the gas evolved at each stage in the warming measured as before. In this way the complete removal of the germane from solution was ensured. The yield of germane at each stage in the reaction was calculated from the quantity of first reactant placed in the flask.

Results.—Addition of lithium aluminium hydride to germanium tetrachloride. The slow addition of lithium aluminium hydride solution to a solution of germanium tetrachloride in tetrahydrofuran at 35° resulted in a vigorous reaction but initially liberated no germane. After the mole ratio of added $LiAlH_4 : GeCl_4$ reached approximately 0·2, germane was steadily evolved until the equimolecular quantity of hydride had been added, when reaction ceased. The addition of excess of hydride gave no further germane. The flask temperature was then raised until the solvent was refluxing gently; some germane was evolved during this heating. In addition to the evolution of germane the initially colourless solution underwent several changes during the addition of the hydride. The solution first became pale yellow and a slight white precipitate appeared, then, as the addition continued, the yellow colour deepened and the precipitate became yellow. Finally an orange solution with a flocculent yellow-orange precipitate was obtained.

This reaction was repeated at 68° and similar results were obtained, except that the colour changes and precipitation occurred earlier than at 35°. A third reaction was carried out at −40° which resulted in a decreased yield of germane and a small quantity of yellow precipitate. On heating, the precipitate dissolved and the solution colour deepened until at 10° a clear red solution resulted which remained clear until 45°. At this temperature an orange precipitate appeared which slowly thickened as the flask was heated to 68°; germane was evolved throughout the heating. The reactions at 35° and −40° after refluxing resulted in approximately the same yields of germane as the reaction at 68°. The yields (based on $GeCl_4$) for these three reactions are plotted against the lithium aluminium hydride added in Fig. 1.

Addition of germanium tetrachloride to lithium aluminium hydride. In the addition of $LiAlH_4$

to $GeCl_4$ the active hydrogen of the hydride does not appear as germane until approximately one-fifth of the hydride has been added. This may be due to a stepwise replacement of chlorine by hydrogen with decreasing rates of reaction in each successive step: $GeCl_4 \longrightarrow GeHCl_3 \longrightarrow GeH_2Cl_2 \longrightarrow GeH_3Cl \longrightarrow GeH_4$. If this is so, then addition of $GeCl_4$ to $LiAlH_4$ may be expected to evolve germane from the beginning of the addition.

The addition of $GeCl_4$ solution to $LiAlH_4$ in tetrahydrofuran at 25° gave a vigorous reaction and as expected germane was evolved immediately the addition commenced. The solution became first yellow then, as addition proceeded, orange. A yellow precipitate appeared which

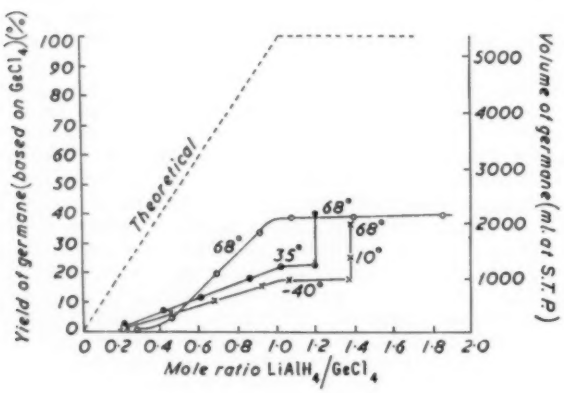

FIG. 1. *Addition of lithium aluminium hydride to germanium tetrachloride.*

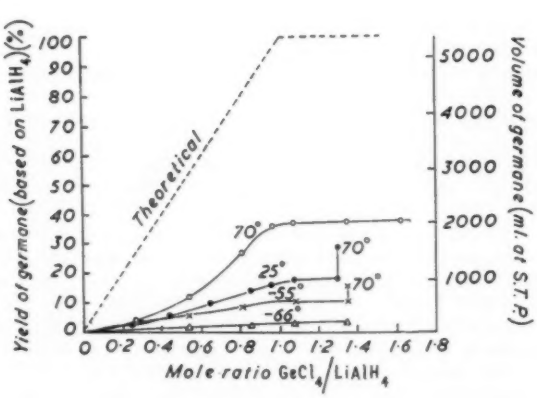

FIG. 2. *Addition of germanium tetrachloride to lithium aluminium hydride.*

also deepened to orange, and reaction finally subsided when equimolecular quantities of reactants were present; no further germane was evolved when $GeCl_4$ was added in excess. The reaction was repeated at 70° and an increase in yield obtained with the appearance of similar colorations and precipitates. A third reaction at −55° gave a poor yield of germane although only a slight quantity of yellow precipitate was present. When the solution was heated with excess of $GeCl_4$, germane was evolved at about 30°. The precipitate dissolved at 45° and remained in solution throughout refluxing. Germane was evolved steadily until 70° but the final yield was much reduced. A further reaction at −66° gave similar results with a further decrease in yield.

The progressive evolution of germane from these four reactions is shown as a function of the addition of $GeCl_4$ in Fig. 2.

Reaction in dioxan. In tetrahydrofuran an increase in temperature favoured the yield of germane. The reaction temperature was limited by the boiling point of the solvent, so the

higher-boiling solvent, dioxan, was employed. Since the solubility of $LiAlH_4$ in dioxan was much lower than in tetrahydrofuran a slurry of $LiAlH_4$ in dioxan was placed in the reaction flask, heated to 30°, and $GeCl_4$ in dioxan slowly added. The reaction was less vigorous than in tetrahydrofuran and germane was liberated from the beginning of the addition. A yellow solid developed early in the reaction. After a slight excess of $GeCl_4$ had been added the flask contents were heated to 96° and refluxed at that temperature for 1 hr. During this time the yellow precipitate became yellow-brown. The yield of germane was 26·4% of theoretical.

Effective solubility of germane in tetrahydrofuran. In order to determine whether the release of germane on heating the final solutions to the reflux temperature of the solvent was due to decreasing solubility of germane in the solvent or to reaction between products, the approximate solubility of germane in tetrahydrofuran was determined under conditions similar to those used in the preparations. A known volume of germane was condensed into a trap by use of liquid nitrogen. The trap temperature was slowly raised and the gaseous germane was bubbled through tetrahydrofuran in the reaction flask. A hydrogen atmosphere at a pressure of 1 atm. was maintained in the reaction flask. The undissolved germane passed into the collection system and was condensed in one of the liquid-nitrogen traps. After all the germane has passed through the solvent the trap and flask were swept out with hydrogen in a similar manner to that used during reactions. The volume of undissolved germane was measured and the volume of dissolved gas calculated from the difference in the original and the collected volumes. The temperature of the solvent was then raised and the germane evolved was collected and its volume measured. The solvent was finally boiled to expel all the germane. Results are as tabulated; a plot of log (volume dissolved) against $1/T(°K)$ is linear.

Temp. (°c)	−73	−40	−30	−10	10	65
$10^3/T$ (°K)	5·00	4·29	4·12	3·80	3·53	3·38
Vol. (ml.) of GeH_4 dissolved in 150 ml. of tetrahydrofuran	2334	351	169	74	33	0

It can be seen that, at the end of the reaction at −40° with approximately 200 ml. of solvent present, the evolution of 419 ml. of germane on heating to 10° could be accounted for by decrease in solubility; but the further evolution of 568 ml. from 10° to 68° cannot be due to decrease in solubility alone. It seems probable, therefore, that some germane is evolved at higher temperatures by reaction between the low-temperature products.

Discussion

A comparison of the reactions between lithium aluminium hydride and other covalent chlorides ($SiCl_4$, BCl_3, $AsCl_3$, etc.), which give the corresponding hydrides in quantitative yield, with the reaction between lithium aluminium hydride and germanium tetrachloride indicates that the latter does not occur in the simple manner indicated by eqn. (1). However, a comparison of the yields of hydride obtained from the chlorides of Group IV elements (Si 99%,[4] Ge 40%, Sn 20% [4]) indicates that the position of germanium is not abnormal. An explanation for the low yield of stannane has been suggested which is based on the easy reducibility of Sn^{IV} to Sn^{II} causing reaction to proceed by two competitive routes (2) and (3).[6]

$$SnCl_4 + LiAlH_4 \longrightarrow Sn(AlH_4)_4$$

$$Sn(AlH_4)_4 - 4AlH_3 \longrightarrow SnH_4 \quad \ldots\ldots\ldots\ldots (2)$$

$$\left.\begin{array}{l} Sn(AlH_4)_4 - 2AlH_3 \longrightarrow Sn(AlH_4)_2 + H_2 \\ Sn(AlH_4)_2 - 2AlH_3 \longrightarrow Sn + H_2 \end{array}\right\} \ldots\ldots\ldots (3)$$

Little stannane was obtained from these reactions since reaction (3) was faster than reaction (2). Silicon is not reduced to a lower valency under these conditions, and a quantitative yield of silane can be obtained from silicon tetrachloride. Germanium is intermediate between silicon and tin in that it does form stable bivalent compounds, but the reduction from Ge^{IV} to Ge^{II} does not occur so readily as for tin.

The low yield and the formation of a yellow germanium compound from the $GeCl_4$—$LiAlH_4$ reaction indicates that in addition to the main reaction producing germane at least one side reaction occurs. Metallic germanium was not produced, indicating that the

[6] Wiberg and Bauer, *Z. Naturforsch.*, 1951, **6b**, 392.

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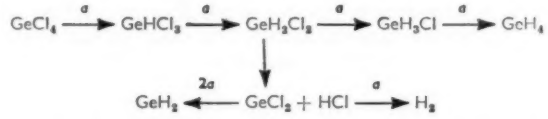
mechanism of the side reaction is not the same as that for the $SnCl_4$—$LiAlH_4$ reaction. A yellow precipitate similar to that obtained with $LiAlH_4$ has also been obtained in a LiH—$GeCl_4$ reaction in tetrahydrofuran, thereby eliminating $Ge(AlH_4)_4$ or $Ge(AlH_4)_2$ as a product of this reaction. This has been confirmed by analysis of the yellow precipitate, which showed little aluminium or lithium present.

The replacement of chlorine by hydrogen is thought to be a stepwise process, and an explanation of the reduced yield of germane has been sought from a consideration of the stability of the compounds intermediate between $GeCl_4$ and GeH_4. All these compounds decompose at room temperature or below. Chlorogermane slowly decomposes at room temperature:[7] $2GeClH_3 \longrightarrow GeH_4 + 2HCl + Ge$. Dichlorogermane decomposes more rapidly, yielding a mixture of products among which Ge, $GeCl_2$, $GeClH_3$, $GeCl_4$, HCl, and hydrogen have been identified.[7] Recently[8] it has been shown that trichlorogermane loses HCl readily at −30°, forming $GeCl_2$. This decomposition seems the most likely to occur under the conditions of the $GeCl_4 \longrightarrow LiAlH_4$ reaction, the side reaction being completed by the replacement of the chlorine atoms in $GeCl_2$ to form a bivalent hydride, the complete scheme being as follows, where *a* represents $\frac{1}{4}LiAlH_4$:



The existence of a yellow germanous hydride insoluble in solvents has been reported;[9] its properties suggest a long-chain polymer $(GeH_2)_x$. It is thought that the yellow colour in solutions at lower temperatures and the precipitation at higher temperatures may be due to the formation of a similar hydride in association with tetrahydrofuran. The precipitation may be due to the conversion of the monomer (stabilized by the solvent) into the polymer in a similar manner to that observed for aluminium hydride.[10]

The above reaction mechanism accounts for the cessation of reaction at the equimolecular ratio of reactants irrespective of the course taken by the reaction. The variations in yield with temperature may be accounted for by different changes in the reaction rate of the two competing reactions with temperature.

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[7] Dennis and Judy, *J. Amer. Chem. Soc.*, 1929, **51**, 2321.
[8] Moulton and Miller, *J. Amer. Chem. Soc.*, 1956, **78**, 2702.
[9] Royen and Schwarz, *Z. anorg. Chem.*, 1933, **211**, 412.
[10] Wiberg, Graf, and Uson, *ibid.*, 1953, **272**, 221.

397. *Preparation of Germane. Part II.* Reaction between Sodium Borohydride and Germanium Tetrachloride.*

By E. D. Macklen.

The preparation of monogermane from the reaction between germanium tetrachloride and sodium borohydride in aqueous solution has been studied at various temperatures. The effect of complete and partial neutralization of the hydrochloric acid liberated by hydrolysis of germanium tetrachloride, together with the rate and order of addition of reactants, has been investigated. Under the best conditions a yield of 79·1% of monogermane was obtained. Nascent hydrogen reduction of Ge^{IV} to metallic germanium is suggested to account for the smaller yield than theoretical.

In Part I * the preparation of litre quantities of monogermane from the reaction between lithium aluminium hydride and germanium tetrachloride in tetrahydrofuran solution was described. However, the yield from this reaction under the best experimental conditions was limited to 40% by the occurrence of side reactions. Difficulties in the preparation of stannane by a similar procedure [1,2] were largely eliminated by replacing lithium aluminium hydride in ether by sodium borohydride in aqueous solution. Using this method, Schaeffer and Emilius [3] obtained an 84% yield of stannane from stannous chloride. This improvement in yield for stannane suggested that a similar improvement in the yield of germane might be expected from the action of aqueous sodium borohydride on germanium tetrachloride.

Experimental

Apparatus and Procedure.—The apparatus and technique were as in Part I.

Materials.—Most of the reactions were carried out in aqueous solution and the following solutions were prepared.

Sodium borohydride solution. 16 g. of commercial sodium borohydride were dissolved in 250 ml. of water, making a solution nominally 1·69M. As such a solution slowly hydrolyses, it was prepared immediately before use. No yields were based on $NaBH_4$, and the active hydride content of solutions was not determined.

Germanium tetrachloride solution. Attempts to prepare an aqueous solution of germanium tetrachloride result in almost complete hydrolysis, and a slurry of germanium dioxide in hydrochloric acid is produced. However, since the dioxide redissolves during reaction this slurry is acceptable. 2·5 ml. of $GeCl_4$ were added to 60 ml. of water, and the equivalent of 0·37 mole of $GeCl_4$/l. of solution was obtained. In all cases where this slurry was used the hydrolysis was carried out in the reaction flask. A solution of 3 ml. of $GeCl_4$ in 100 ml. of tetrahydrofuran was also prepared so that $GeCl_4$ could be added to $NaBH_4$ by means of a tap funnel.

Results.—Since the addition of germanium dioxide slurry in controllable quantities through a tap funnel was not possible, the initial reactions were carried out with the slurry in the flask. A reasonable yield of a gas condensable in liquid nitrogen was obtained from a preliminary reaction, and although vapour-pressure measurements on this gas indicated monogermane the absence of diborane could not be assumed, although the preparation of diborane from aqueous solution was highly unlikely. Pyrolysis of the gas gave a purity for the germane of 98·4% and chemical analysis of the residue from pyrolysis confirmed the absence of boron and the presence of germanium only.

In the following reactions all yields of germane were based on the original $GeCl_4$ content, and even for the addition of $GeCl_4$ in tetrahydrofuran to aqueous $NaBH_4$ the final yield was calculated from the $GeCl_4$ added rather than from the $NaBH_4$.

Addition of sodium borohydride to germanium tetrachloride. (a) *Effect of temperature.* The addition of $NaBH_4$ to the dioxide slurry was carried out at 20°, 60°, and 80° and the volumes

* Part I, preceding paper.

[1] Finholt, Bond, Wilzbach, and Schlesinger, *J. Amer. Chem. Soc.*, 1947, **69**, 2692.
[2] Wiberg and Bauer, *Z. Naturforsch.*, 1951, **6**b, 392.
[3] Schaeffer and Emilius, *J. Amer. Chem. Soc.*, 1954, **76**, 1203.

of germane liberated during the addition were measured. The values are shown in Fig. 1. It can be seen that although lower temperatures favour the yield of germane, little difference is apparent between the yields at 20° and 60° whereas a pronounced difference is observed at 80°. After the reaction at 20° the flask contents were heated to 60° but no further germane was evolved. The reactions at 60° and 80° produced a mirror of metallic germanium on the wall of the flask below the liquid level, the weight of which indicated that all germanium not evolved as germane had been thus deposited.

(b) *Effect of rate of addition of* $NaBH_4$. The rate of addition of the hydride was kept at

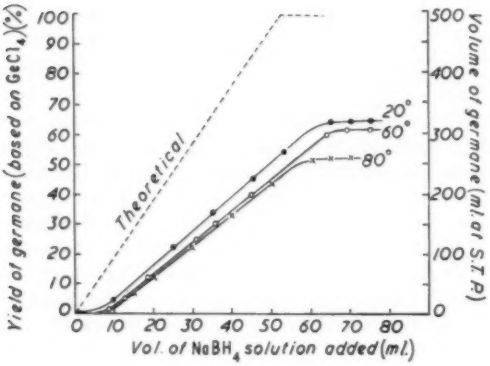


FIG. 1. *Effect of temperature during addition of* $NaBH_4$ *to* $GeCl_4$.

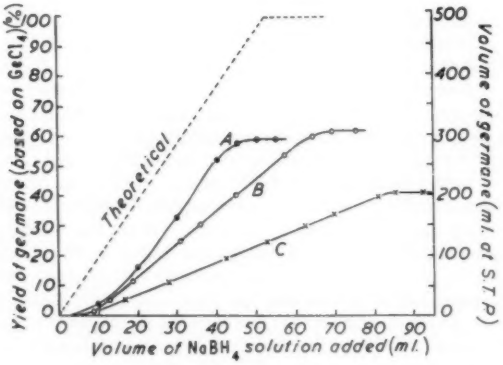


FIG. 2. *Effect of varying concentration of* HCl *in* GeO_2 *slurry at* 60°.
A, HCl = 0·72N; *B*, HCl = 1·46N; *C*, HCl = 2·92N.

approximately 1 ml. of solution per minute in order to keep the temperature constant. The effect of adding the second reactant very rapidly was investigated by increasing this rate of addition to 20 ml./min. Reaction commenced at 25° but the temperature rapidly rose to 70° during the first few minutes of addition, and a final yield of 29% of germane was obtained. This was a large reduction in the yield compared with those obtained for slower addition, and all other reactions were carried out with addition of 1 ml./minute.

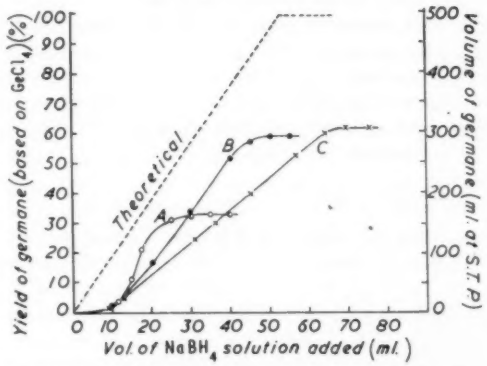
(c) *Effect of acid concentration.* The hydrolysis of germanium tetrachloride by water resulted in a slurry of germanium dioxide in 1·46N-hydrochloric acid. The effect of doubling the acid concentration by addition of hydrochloric acid was investigated. It was found that the quantity of $NaBH_4$ required to complete the reaction was increased; and also that the yield of germane was reduced to 41% at 60°. Neutralization of half of the hydrochloric acid with sodium hydroxide or ammonia had little influence on the yield of germane (60% at 60°), but decreased by a third the quantity of $NaBH_4$ required to complete the reaction. Complete neutralization of the acid almost entirely prevented the formation of germane (yield 6% at

60°), indicating that some hydrochloric acid is required for reaction. The evolution of germane with $NaBH_4$ addition for slurries of different acid concentrations is shown in Fig. 2.

An alternative method of reducing the effect of the hydrochloric acid on $NaBH_4$ was the use of solutions of $NaBH_4$ made alkaline with sodium hydroxide. This had the additional advantage of stabilizing the borohydride solution so that the solution could be stored without appreciable hydrolysis. The effect of alkaline $NaBH_4$ on the reaction was similar to that of partial neutralization of the acid before reaction. For 1·2N-sodium hydroxide a decrease in the quantity of $NaBH_4$ required without appreciable alteration in the yield of germane was obtained, but 2·38N-alkali caused a more rapid evolution of germane and reduced the yield to 33% at 60°. These effects are shown in Fig. 3.

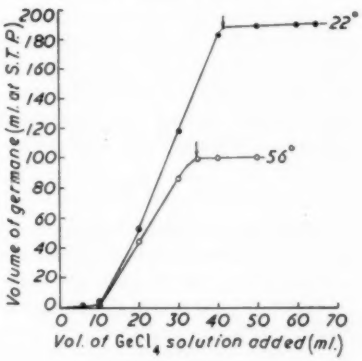
Addition of germanium tetrachloride to sodium borohydride. To obtain a more complete picture of the reaction, the addition of $GeCl_4$ to sodium borohydride was required. This was accomplished by the use of a solution of germanium tetrachloride in tetrahydrofuran placed in the tap funnel which was added slowly to 4 g. of $NaBH_4$ in 75 ml. of water in the reaction flask.

FIG. 3. *Effect of varying concentration of* NaOH *in* $NaBH_4$ *solution at* 60°.



A, NaOH = 2·38N; *B*, NaOH = 1·21N; *C*, no NaOH.

FIG. 4. *Effect of temperature during addition of* $GeCl_4$ to $NaBH_4$.



This reaction was carried out at 22° and 56° and the evolution of germane is plotted against the addition of $GeCl_4$ in Fig. 4. Reaction in both cases had ceased at the point indicated by the arrow, and the yield of germane at this point was calculated from the quantity of $GeCl_4$ added. Values of 79·1% at 22° and 49·7% at 56° were obtained.

For both of these reactions an orange precipitate was formed which remained between the water layer and the tetrahydrofuran layer in the flask. The properties of this precipitate indicated that it was similar to the bivalent reduction product of the reaction of germanium tetrachloride with lithium aluminium hydride in tetrahydrofuran.

Reaction in tetrahydrofuran. A slurry of 3 g. of $NaBH_4$ in 75 ml. of tetrahydrofuran was placed in the reaction flask and the temperature kept at 25°. A solution of 3 ml. of $GeCl_4$ in 100 ml. of tetrahydrofuran was slowly added, but little germane was evolved. After 50 ml. of $GeCl_4$ solution had been added the addition was stopped and the volume of germane collected was found to be 36·1 ml., corresponding to a yield of 12·4% based on $GeCl_4$. The addition of 7 ml. of water at this stage increased the yield to 40·3% after a vigorous reaction. The further addition of 43 ml. of water increased the yield to 43·7%. The orange germanium reduction product was again formed during the reaction.

The low yield of germane from the reaction in tetrahydrofuran may be partially due to the inability of the $NaBH_4$ to ionize to any extent, but the presence of water may also be necessary to complete the formation of GeH_4 from the primary reaction product of $GeCl_4$ and $NaBH_4$.

DISCUSSION

The reaction of sodium borohydride with germanium tetrachloride in an aqueous medium provides one of the most efficient methods of preparing monogermane in litre quantities

with reasonable yields. However, the emergence of metallic germanium as a reaction product indicates that the yield of germane is reduced by at least one side reaction. By analogy with other reactions involving $NaBH_4$ it seems likely that the primary reaction producing germane is a two-stage reaction in which germanium borohydride is first formed by the action of sodium borohydride on germanium tetrachloride, then decomposed by the water, evolving monogermane:

$$GeCl_4 + 4NaBH_4 \longrightarrow Ge(BH_4)_4 + 4NaCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$Ge(BH_4)_4 + 12H_2O \longrightarrow GeH_4 + 4B(OH)_3 + 12H_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

In this way the water performs two functions, initially promoting the formation of BH_4^- ions for reaction (1), and finally decomposing the $Ge(BH_4)_4$. The low yield of germane from the reaction in tetrahydrofuran together with the immediate evolution of germane after the addition of water to this system illustrate the necessity for the presence of water if reasonable yields of germane are to be obtained.

The second reaction sequence which occurs in this system involves the reduction of quadrivalent germanium to the free metal. This mode of behaviour has been observed in other systems; silver, bismuth, arsenic, and antimony salts have been reduced to free metals by interaction with sodium borohydride,[4] and Ce^{IV}, Cr^{VI}, Tl^{III}, Hg^{II}, and Fe^{III} reduced to the next lower stable valency.[5] It seems likely that the reduction of Ge^{IV} to Ge^{II} and finally to metallic germanium in aqueous solutions occurs not by direct reaction with $NaBH_4$ but by means of nascent hydrogen evolved either in reaction (2) or by the reaction of hydrochloric acid (obtained by hydrolysis of $GeCl_4$) with $NaBH_4$:

$$NaBH_4 + HCl + 3H_2O \longrightarrow NaCl + B(OH)_3 + 4H_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

In solutions of tetrahydrofuran the occurrence of the orange bivalent germanium reduction product indicates that the reduction of germanium ceases at Ge^{II}, no metallic germanium having been found in such systems.

Since the evolution of hydrogen from aqueous sodium borohydride solutions increases rapidly with increase in temperature,[6] the reduction in yield of germane with increase in temperature may be explained in terms of the increased availability of nascent hydrogen thus favouring the reduction of Ge^{IV} to metallic Ge. The reduction of germane yield from germanium dioxide slurries containing additional hydrochloric acid may be similarly explained by the increased availability of nascent hydrogen.

The author thanks Dr. S. G. Foord for advice and criticism.

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[4] Schlesinger and Brown, U.S.P. 2,461,661 (Feb. 15th, 1949).
[5] Schaeffer and Frank, unpublished work.
[6] Schlesinger, Brown, Finholt, Gilbreath, Hoekstra, and Hyde, *J. Amer. Chem. Soc.*, **1953**, **75**, 218.

398. *Distortion in the Perovskite-type Structures of Lanthanon Mixed Oxides,* $LnMO_3$.

By J. A. W. Dalziel.

A qualitative explanation is given of the distortion found in perovskite-type structures of the lanthanon mixed oxides with general formula $LnMO_3$. The changes in lattice symmetry which occur as the distortion increases arise mainly from the non-ideality of the radius ratios of the ions involved. The influence of partial covalent character in M–O linkages on the stabilisation of the structures is demonstrated by reference to the three series $LnAlO_3$, $LnFeO_3$, and $LnGaO_3$. The partial covalent character tends to increase as the lanthanide contraction proceeds along each series. It is most significant if the common M ions have partly filled *d* shells, when the utilisation of inner orbitals may produce an increase in polarisation energy sufficient to extend the range over which the perovskite lattice tolerates distortion. This effect occurs in the $LnFeO_3$ series and should be more pronounced in the $LnCoO_3$ series.

Perovskite-type Structures of Lanthanon Mixed Oxides.—The crystal lattice of an ideal perovskite (AMO_3) has primitive cubic symmetry with all the ions in special positions in the unit cell, *viz.*, A = $\frac{1}{2}\frac{1}{2}\frac{1}{2}$; M = 000; O = $\frac{1}{2}00,0\frac{1}{2}0,00\frac{1}{2}$. This corresponds to layers of composition $(AO_3)_n$, normal to the cube diagonals of the unit cell, arranged in the cubic order (*abcabc*-) with all octahedral holes formed by oxygen ions occupied by *n*M ions.[1] Since there are no variable parameters in the ideal lattice the non-ideality of the radius ratios and the polarisation of ions is accommodated by ***distortion*** to related lattices of lower symmetry. The limits over which the perovskite lattice can tolerate the non-ideality of ions is often specified by an empirical tolerance factor (*t*) derived from the geometry of the cubic cell and the radii of the ions (*r*), *viz.*,

$$t = (r_A + r_O)/\sqrt{2}(r_M + r_O)$$

For most perovskite-type oxides the values of *t* lie between about 1·1 and 0·8.

The structures of many lanthanon mixed oxides of general formula $LnMO_3$ which are of the perovskite-type have been established in some detail by the work of Geller and his co-workers.[2,3,4] The three series $LnAlO_3$, $LnFeO_3$, and $LnGaO_3$, where Ln represents a series of lanthanons and the M ions exhibit different types of electronic configuration, are of particular interest in the investigation of the factors which govern distortion. I have confirmed Geller and his co-workers' results for compounds belonging to these three series, using *X*-ray powder methods, and have established the structures of $DyAlO_3$ and $DyFeO_3$.[5] A summary of the combined data is given in Table 1. Each series shows a common pattern of distortion away from the ideal cubic lattice through rhombohedral towards orthorhombic symmetry as the lanthanide contraction proceeds. This appears to hold for all $LnMO_3$ perovskites, with the possible exception of the series $LnCoO_3$, which will be discussed later. The electronic configurations of the M ions have no apparent influence on the symmetries assumed by the distorted structures but they do influence the limits over which the perovskite lattice is stable. Thus, the lower limit of *t* for the $LnAlO_3$ and $LnGaO_3$ series lies in the region of 0·90 and 0·91 but extends beyond 0·85 for the $LnFeO_3$ series.

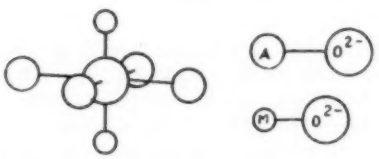
Factors which influence the Distortion.—It is convenient to discuss the factors which influence the distortion of the perovskite-type lattices of the lanthanon mixed oxides by separating that which arises from the non-ideality of the radius ratios of ions (ionic distortion) from that due to the partial covalent character of M–O linkages (covalent distortion).

[1] Wells, "Structural Inorganic Chemistry," Oxford Univ. Press, 1950.
[2] Geller, *J. Chem. Phys.*, 1956, **24**, 1236.
[3] Geller *et al.*, *Acta Cryst.*, 1956, **9**, 563, 1019; 1957, **10**, 161, 234.
[4] Reimeika, *J. Amer. Chem. Soc.*, 1956, **78**, 4259.
[5] Dalziel and Welch, *Acta Cryst.*, in the press.

Other factors, such as the partial covalent character of Ln–O linkages, will be neglected in the discussion which is therefore approximate. This method of treatment is related to that used by Megaw [6,7] for the $A^{I}M^{V}O_3$ and $A^{II}M^{IV}O_3$ subgroups of the perovskites.

According to Megaw the symmetry assumed by $A^{I}M^{V}O_3$ and $A^{II}M^{IV}O_3$ perovskites is largely dependent upon the partial covalent character of their M–O linkages, *i.e.*, covalent distortion. In the $LnMO_3$ subgroup of the perovskites covalent distortion should be less important. This follows from the reduced " electrostatic bond strengths " in the M–O linkages and the more symmetrical cationic charge distribution around the oxygen ions in $LnMO_3$ perovskites, as shown in Fig. 1. That the polarisation of the oxygen ions in the nearly cubic structure of $LaAlO_3$ is smaller than in the cubic $A^{II}M^{IV}O_3$ perovskites is demonstrated by the following argument. A cubic perovskite lattice irrespective of polarisation must satisfy the geometrical relationship: $(r_A + r_O)/\sqrt{2} = (r_B + r_O) = a/2$, where (a) is the length of the unit-cell edge. The values of the oxygen-ion radius can then

FIG. 1. *Asymmetry of cationic charge distribution around oxygen ions in the perovskite lattice and change in electrostatic bond strengths in different subgroups.*



	Electrostatic bond strengths		
	$A^{I}M^{V}O_3$	$A^{II}M^{IV}O_3$	$Ln^{III}M^{III}O_3$
A	$\frac{1}{12}$	$\frac{1}{6}$	$\frac{1}{4}$
M	$\frac{5}{6}$	$\frac{2}{3}$	$\frac{1}{2}$

be derived in two ways, *viz.*, $r_O = a/2 - r_B$ or $r_O = (a/\sqrt{2}) - r_A$. Since smaller cations will tend to be less deformed by polarisation than larger anions, the substitution of spherical values for the cationic radii in these equations to obtain numerical values for r_O is justified to an approximation. The values of r_O for $LaAlO_3$ and the cubic $A^{II}M^{IV}O_3$ perovskites,[8] derived in this way, are shown in Table 2. The cationic radii used [9] have been corrected

TABLE 1. *Summary of crystallographic data for perovskite-type lanthanon mixed oxides* $LnAlO_3$, $LnFeO_3$, *and* $LnGaO_3$, *where* Ln = La, Nd, Gd, *and* Dy.

Mixed oxide	Space lattice	Z	Cell dimensions (Å) a	b	c	V	Space group	Transitions
$LaAlO_3$	Rhombohedral	2	5·357 $\alpha = 60{\cdot}10°$			54·5	$R\bar{3}m$	Cubic above 435° c
$NdAlO_3$	Rhombohedral	2	5·286 $\alpha = 60{\cdot}41°$			52·7	$R\bar{3}m$	
$GdAlO_3$	Orthorhombic	4	5·247	5·304	7·447	51·8	*Pbnm*	
$DyAlO_3$	Orthorhombic	4	5·215	5·311	7·407	51·3	*Pbnm*(?)	
$LaFeO_3$	Orthorhombic	4	5·556	5·565	7·862	60·8	*Pbnm*	Rhombohedral above 980°c
$NdFeO_3$	Orthorhombic	4	5·441	5·573	7·753	58·8	*Pbnm*	
$GdFeO_3$	Orthorhombic	4	5·346	5·616	7·668	57·6	*Pbnm*	
$DyFeO_3$	Orthorhombic	4	5·304	5·600	7·621	56·6	*Pbnm*(?)	
$LaGaO_3$	Orthorhombic	4	5·496	5·524	7·787	59·2	*Pbnm*	Rhombohedral above 875° c
$NdGaO_3$	Orthorhombic	4	5·426	5·502	7·706	57·5	*Pbnm*	
" $GdBaO_3$ "	Garnet phase							
" $DyGaO_3$ "	Garnet phase							

Z = number of formula weights per unit cell.
V = volume occupied by one formula weight (Å³).

in the case of A and Ln ions for twelve-fold co-ordination. The data in the table show in particular that the oxygen ions in $LaAlO_3$ are nearly spherical and therefore are not polarised. This contrasts markedly with the case of $A^{II}M^{IV}O_3$ perovskites.

It is concluded that the least distorted $LnMO_3$ perovskites have structures which are

[6] Megaw, *Acta Cryst.*, 1952, **5**, 739; 1954, **7**, 187.
[7] Megaw, " Ferroelectricity in Crystals," Methuen, London, 1957.
[8] Megaw, *Proc. Phys. Soc.*, 1946, **58**, 133.
[9] Ahrens, *Geochim. Cosmichim. Acta*, 1952, **2**, 155.

dependent primarily upon the effects of ionic distortion on the ideal lattice. As the lanthanide contraction proceeds along a series the distortion increases and the volumes occupied by the formula weights exhibit a regular decrease (Table 1). The significance of

TABLE 2. *Values for the radii of the oxygen ions calculated from the dimensions of cubic perovskites.*

	r_O (Å)	
$A^{II}M^{IV}O_3$	from $r_B + r_O$	from $r_A + r_O$
$SrTiO_3$	1·27	1·54
$SrZrO_3$	1·26	1·67
$SrSnO_3$	1·30	1·62
$BaSnO_3$	1·34	1·44
$BaZrO_3$	1·30	1·50

	r_O (Å)	
$LnBO_3$	from $r_B + r_O$	from $r_A + r_O$
$LaAlO_3$	1·39	1·44
($NdAlO_3$	1·37	1·41)
($LaFeO_3$	1·32	1·53)

the relative decreases in the different series will be considered in more detail later; a decrease in the volume occupied by a formula weight will tend to increase the polarisation of the ions. Hence, covalent distortion will tend to increase as the lanthanide contraction proceeds along each series. Now an estimate of the relative importance of ionic and

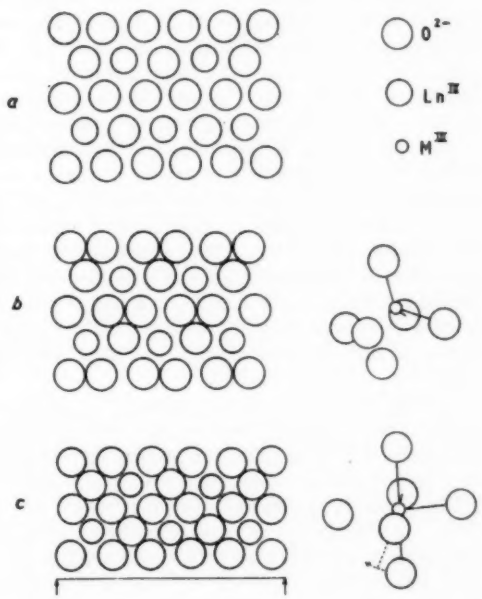


FIG. 2. $(LnO_3)_n$ *Layers with* r_{Ln}/r_O *less than unity, and octahedral sites for* M *ions when layers are arranged in the order abcabc-.*

a. Regular layer of $R\bar{3}m$, $Z = 1$ lattice.
b. Less regular rearrangement (projection on rhombohedral (111) plane and quasi-sp^2 environment of M ions.
c. Layer of *Pmmm*, $Z = 2$ lattice, derived by compression from 2*a* [projection on orthorhombic (101) plane] and quasi-sp^3 environment of M ions.

covalent distortion can be made by the consideration of (*a*) the extent to which increases in ionic distortion can produce the observed changes from cubic through rhombohedral to orthorhombic symmetry in the perovskite lattice, and (*b*) the extent to which covalent distortion is present in the representative series $LnAlO_3$, $LnFeO_3$, and $LnGaO_3$.

Ionic Distortion.—In the purely ionic distortion of the perovskite lattice the ions must be represented as rigid spheres, since their deformation would represent covalent distortion. When such ions are formed into $(LnO_3)_n$ layers in the ideal way they are not close-packed if the radius ratio r_{Ln}/r_O is less than unity. Moreover, if the ideal lattice is made from the cubic arrangement of these layers no more than four oxygen ions make contact with each Ln ion. Thus, when r_{Ln}/r_O is less than unity this ideal arrangement is unstable with respect to a less symmetrical one which brings more oxygen ions into contact with each Ln ion and hence increases the coulombic lattice energy.

Such an arrangement occurs when the perovskite lattice assumes rhombohedral symmetry. Megaw [6] has described how the rhombohedral lattice is produced when a force of compression acts parallel to one cube diagonal of the ideal lattice. This brings the $(LnO_3)_n$ layers which are normal to the force closer together, until each Ln ion is in contact with the six oxygen ions of the neighbouring layers. To do this without deforming the oxygen ions the layers which are normal to the force of compression must be opened out. The most regular way of doing this for one $(LnO_3)_n$ layer is shown in Fig. 2*a*. When such layers are arranged in the order *abcabc*- and *n* M ions are placed in the unsymmetrical octahedral sites available, a rhombohedral lattice ($R\bar{3}m$, $Z = 1$) is obtained which is rather more symmetrical than those found for $LnMO_3$ perovskites with rhombohedral distortion. Rhombohedral lattices of lower symmetry can be formed by purely ionic distortion if a less regular arrangement occurs in the layers. Thus, when $(LnO_3)_n$ layers of the kind shown in Fig. 2*b* are arranged, as before, in the order *abcabc*- the rhombohedral unit cell is no longer perfectly centrosymmetrical. It is of interest because the lattice contains octahedral holes, shown in Fig. 2*b*, which would tend to be compatible with sp^2 hybrid character in the M–O linkage. According to Geller and his co-workers the rhombohedral $LnMO_3$ perovskites have two formula weights in their unit cells. Lattices of this kind require a repeating pattern of six layers and a less regular arrangement must occur within the layers. Layers of the kind shown in Fig. 2*b* can be arranged in a six-fold repeating pattern *ab'ca'bc'*-, where the three layers denoted by primes have been turned so that their groups of oxygen ions " point " in the opposite direction from those in the other three layers. This arrangement produces a lattice which contains two kinds of octahedral hole for occupation by M-type ions and is unsatisfactory from this point of view. No more satisfactory arrangement of layers to give a six-fold repeating pattern has been found. However, the lattices of the rhombohedral $LnMO_3$ perovskites are sufficiently close to these lattice models to make it reasonable to conclude that their distortion arises mainly from the non-ideality of the radius ratios of the ions involved. Some confirmation that the distortion is essentially ionic is provided by the observation [3] that the transition from rhombohedral to cubic $LaAlO_3$ is a higher than first-order change. The transition of the related structure of nickel oxide, which is from rhombohedral to cubic symmetry by a higher than first-order change, has also been attributed to the non-ideality of the ionic radii.[10]

Similarly orthorhombic symmetry is produced by ionic distortion as the radius ratio r_{Ln}/r_O departs further from unity. An orthorhombic lattice is formed when a force of compression is allowed to act parallel to a face diagonal of the cubic cell.[6] This force can be resolved into the rhombohedral force of compression and an additional force which acts in the plane of the layers. A layer which has been derived in this way from Fig. 2*a* is shown in Fig. 2*c*. The octahedral holes available for M-type ions when these layers are arranged in the order *abcabc*- would tend to be compatible with sp^3 hybrid character in M–O linkage if they are slightly modified, as shown in Fig. 2*c*. The space-group symmetry of the orthorhombic lattice is *Pmmm*, $Z = 2$. This is the holosymmetrical space-group from which it should be possible to derive *Pbnm*, $Z = 4$, which has been reported by Geller [2] for $GdFeO_3$ and other orthorhombic perovskites, if a repeating pattern of six less regular $(LnO_3)_n$ layers is used. Thus, it appears that the orthorhombic symmetry found in the more distorted $LnMO_3$ perovskite lattices is not inconsistent with the increased non-ideality of the radius ratios of the ions involved. That orthorhombic symmetry occurs commonly, irrespective of the electronic configuration of the M-type ions involved, tends to support the view that ionic distortion is important even in the most distorted $LnMO_3$ perovskites. However, there is evidence that covalent distortion also is present to a significant extent in at least some orthorhombic lattices.

Covalent Distortion.—If the lattices of a series of $LnMO_3$ perovskites with the M ions in common are all essentially ionic in character, the volumes occupied by their formula

[10] Rooksby, *Acta Cryst.*, 1948, **1**, 226.

weights should decrease as the lanthanide contraction proceeds along the series, but to a smaller extent than would be predicted from the decreases in the volumes of the lanthanon ions alone, because the packing deviates increasingly from close-packing. The relative ionic character in the different series can therefore be tested by a plot of the volumes occupied by one formula weight against those occupied by the respective lanthanon ions in twelve-fold co-ordination. Fig. 3 shows plots of V_{Ln} against V_{LnMO_3} (full lines) and against $V_{LaMO_3}-(V_{La}-V_{Ln})$ (broken lines) for the three series $LnAlO_3$, $LnFeO_3$, and $LnGaO_3$. The deviation between full and broken curves is in the direction expected for ionic distortion only for the $LnAlO_3$ and $LnGaO_3$ series; it is reversed for the $LnFeO_3$ series. This is positive evidence that the increase in polarisation energy, *i.e.*, covalent distortion, in the $LnFeO_3$ series is of a different order of magnitude from that in the other two series and is sufficient to overcome the non-ideality of ionic packing in the more distorted lattices. The larger increase in the polarisation energy, which will tend to stabilise the perovskite lattice, accounts for the lower limit of t in the $LnFeO_3$ series.

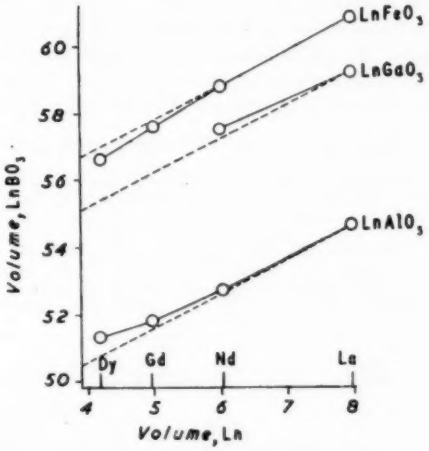


FIG. 3. *Relationships between the volumes of formula weights of* $LnMO_3$ *perovskites and the volumes of their lanthanon ions (full lines) compared with* $V_{LaMO_3}-(V_{La}-V_{Ln})$ *(broken lines) in* Å^3.

Significant partial covalent character in M–O linkages would also account for the observation that transitions from orthorhombic to rhombohedral symmetry may be first-order changes.[3]

The reason for the differences between the polarisation energies in series of $LnMO_3$ perovskites can be understood when the atomic orbitals of the M ions, which can be utilised in the formation of partial-covalent M–O linkages, are considered. The tervalent ions of aluminium, iron, and gallium, which have an inert-gas, a half-filled *d* shell, and an eighteen-electron configuration respectively, have been chosen as representative M ions from this point of view. If the polarisation energy in a perovskite lattice is small the M ions are subjected to a relatively weak electrostatic crystal-field effect.[11] In this case all types of M ion, irrespective of their electronic configurations, will tend to utilise their outer atomic orbitals and M–O linkages with relatively weak partial covalent character will be formed. It is reasonable to suppose that the outer sp^2 and sp^3 hybrid orbitals will be utilised successively as the lanthanide contraction proceeds along any series. Already, it has been seen that sp^2 and sp^3 hybrid character in M–O linkages would tend to be nearly compatible with rhombohedral and orthorhombic distortion respectively. The utilisation of these outer hybrid orbitals therefore should not produce appreciable changes in the symmetry of perovskite lattices which are subjected primarily to ionic distortion, as described above. However, if outer orbitals only are involved in the formation of M–O linkages Goodenough

[11] Gillespie and Nyholm, *Quart. Rev.*, 1957, **11**, 339.

and Loeb [12] consider that partial covalent character should increase in the order Al < Fe < Ga. This is not in accordance with the trends shown in Fig. 3 although it provides a reason for the observed tendency of gallium ions to favour tetrahedral co-ordination with oxygen ions in the ready formation of garnet phases. The discordance is removed if it is assumed that in the $LnFeO_3$ series the larger increase in polarisation energy arises by the interaction of the ferric ions with a relatively strong electrostatic crystal field. Then the inner orbitals of the ferric ions can be utilised in the formation of Fe–O linkages with significant partial covalent character. The configuration of the ferric ion will alter from its spin-free state ($d_\epsilon^3 d_\gamma^2$) towards the spin-paired state ($d_\epsilon^5 d_\gamma^0$) as the lanthanide contraction proceeds and the d_γ orbitals can then be utilised, probably for the formation of $d_\gamma^2 sp^3$ hybrid orbitals. The utilisation of inner orbitals by tervalent first-row transition metal ions should be most pronounced in the case of cobalt.[13] In the series $LnCoO_3$ it would be expected that, as the polarisation energy increases along the series, there should be a large tendency to form symmetrical octahedral Co–O linkages with appreciable covalent character. This effect might even be sufficient to act as a restorative force and reduce the distortion of the perovskite lattice as the lanthanide contraction proceeds. It is significant therefore that the distortion in the $LnCoO_3$ series is anomalous; the rhombohedral distortion in $LaCoO_3$ is reported [14] to decrease as the lanthanide contraction proceeds until at $SmCoO_3$ the perovskite lattice is nearly cubic.[15]

I thank Dr. A. J. E. Welch for helpful advice.

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LONDON, S.W.7. [*Received, January 19th*, 1959.]

[12] Goodenough and Loeb, *Phys. Rev.*, 1955, **98**, 391.
[13] Griffith and Orgel, *Quart. Rev.*, 1957, **11**, 381.
[14] Wold, Post, and Banks, *J. Amer. Chem. Soc.*, 1957, **79**, 6365.
[15] Wold and Ward, *J. Amer. Chem. Soc.*, 1954, **76**, 6060.

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399. *The Chemistry of ψ-Santonin. Part XI.* Its Absolute Configuration.*

By WESLEY COCKER, T. B. H. MCMURRY, and (in part) L. O. HOPKINS.

Previous configurational assignments to the centres at 7, 8, and 10 in ψ-santonin (I) have been confirmed by relating it to tetrahydroalantolactone (VII). The steric formula for tetrahydro-ψ-santonic acid (II) has been justified. The stereochemistry of these compounds at position 11 is discussed.

IN a preliminary communication [1] we described the conversion of ψ-santonin [2-4] (I) through tetrahydro-ψ-santonic acid [4,5] (II) into the acid (V), which we now show to be 8α-hydroxy-4 : 5 : 11α(H)-eudesman-13-oic acid. The latter acid was previously obtained [6] from tetrahydroalantolactone whose absolute configuration at all centres except that at $C_{(11)}$ (but see below) has been shown to be as in (VII).[6,7] We now give details of the investigations previously outlined.[1]

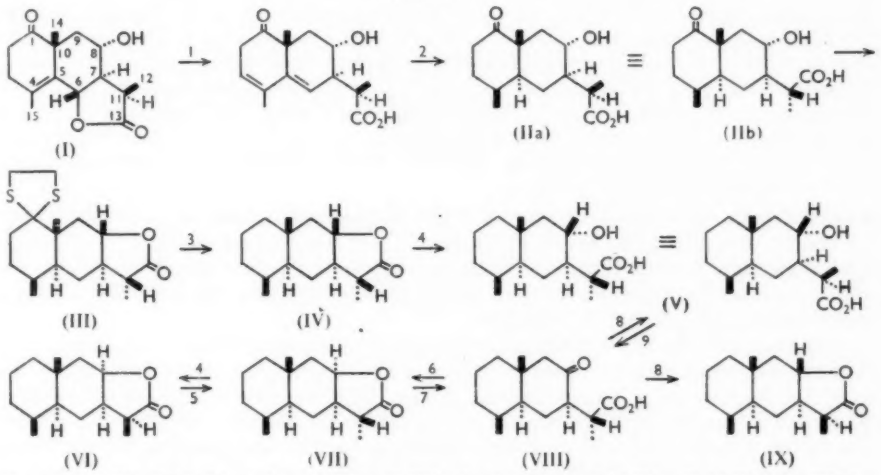
* Part X, *J.*, 1956, 1828. In the present paper we use Cocker and Cahn's nomenclature (*Chem. and Ind.*, 1955, 384). In the case of the acids (*e.g.*, II, III) the 11(H) is referred to as α- or β- by reference to the 11(H) of the angular lactones (*e.g.*, I).

[1] Cocker and McMurry, *Proc. Chem. Soc.*, 1958, 147.
[2] Chopra, Cocker, Cross, Edward, Hayes, and Hutchison, *J.*, 1955, 588.
[3] Dauben and Hance, *J. Amer. Chem. Soc.*, 1955, **77**, 606.
[4] Chopra, Cocker, Edward, McMurry, and Stuart, *J.*, 1956, 1828.
[5] Cocker and Lipman, *J.*, 1949, 1170.
[6] Tsuda, Tanabe, Iwai, and Funakoshi, *J. Amer. Chem. Soc.*, 1957, **79**, 5721; cf. Tanabe, *Pharm. Bull. (Japan)*, 1958, **6**, 214, 218.
[7] Benešová, Sýkora, Herout, and Šorm, *Chem. and Ind.*, 1958, 363.

Tetrahydro-ψ-santonic acid [4,5] (II) was converted (Scheme A) into the ethylene dithioketal (III) by treatment with ethanedithiol and the boron trifluoride–ether complex,[8] lactonisation taking place in the process. When the dithioketal was treated with Raney nickel in boiling dioxan, the product (IV) was a gum, but on hydrolysis with 10% methanolic potassium hydroxide this gave pure 8α-hydroxy-4 : 5 : 11α(H)-eudesman-13-oic acid (V), identical with a sample prepared by the method of Tsuda *et al.*[6] from tetrahydroalantolactone (VII) by way of the keto-acid (VIII). We should, however, mention that our specimens melted at 183° and 185° respectively, some 10° higher than the quoted figure.[6]

The reactions involved in the conversion of ψ-santonin (I) into the hydroxy-acid (V) could not affect the configuration at positions 7, 8, and 10. Hence, since the absolute

Scheme A.



Reagents: 1, H^+. 2, H_2–Pd. 3, Ni. 4, OH^-. 5, OMe^- for short time. 6, $NaBH_4$. 7, (*a*) OH^-, (*b*) CH_2N_2, (*c*) CrO_3, (*d*) OH^-. 8, Na–Pr^iOH. 9, (*a*) CH_2N_2, (*b*) CrO_3, (*c*) OH^-.

configuration of the lactone (VII) at all centres except $C_{(11)}$ is known,[6,7] ψ-santonin (I) must have the absolute configurations shown at these centres, and this assignment is in accord with our previous predictions.[2,4] Likewise, tetrahydro-ψ-santonic acid (II) has the previously predicted [4,5] configurations at centres 4, 5, 7, 8, and 10. The configuration at $C_{(10)}$ agrees with the assignment derived [9] from the rotatory dispersion curve of tetrahydro-ψ-santonic acid.

Recent work by Sumi, Dauben, and Hayes [10] confirmed our stereochemical assignments for ψ-santonin by relating it to artemisin. Artemisin has been shown [11] to be 8α-hydroxysantonin and hence has the absolute configuration shown in (X). Sumi *et al.*[10] used the reactions shown in Scheme B for the conversion of artemisin into the lactone (XI) which had previously [12] been obtained from anhydro-ψ-santonic acid [4] (XII), a rearrangement product of ψ-santonin (I); in this way they demonstrated that ψ-santonin has the same configuration as artemisin at positions 7, 8, and 11.

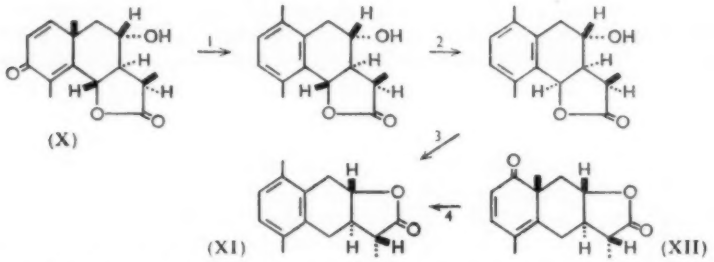
On combining our investigations with those of Sumi *et al.* it is clear that the steric

[8] Fieser, *J. Amer. Chem. Soc.*, 1954, **76**, 1945.
[9] Djerassi, Riniker, and Riniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6362; Djerassi and Marshall, *ibid.*, 1958, **80**, 3987.
[10] Sumi, Dauben, and Hayes, *ibid.*, p. 5704.
[11] Sumi, *Proc. Japan Acad.*, 1956, **32**, 684; 1957, **33**, 153; *Pharm. Bull. (Japan)*, 1957, **5**, 187; *J. Amer. Chem. Soc.*, 1958, **80**, 4869.
[12] Dauben, Hance, and Hayes, *ibid.*, 1955, **77**, 4609.

formula for ψ-santonin is (I),[2,4] except that the configuration at position 6 awaits direct establishment.

Mention can now be made of the configuration at position 11 of ψ-santonin (I) and its derivatives and of tetrahydroalantolactone (VII). Asselineau, Bory, and Lederer [13] have shown that when the last compound (VII) (m. p. 148°, $[\alpha]_D$ +16°) is heated at 210° with

Scheme B.

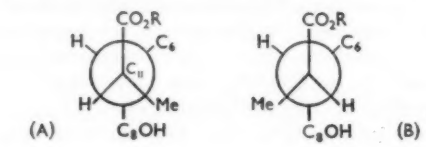


Reagents: 1, (*a*) NH_2·OH, (*b*) Zn–H_2SO_4. 2, (*a*) OH^-, (*b*) H^+. 3, Zn–AcOH. 4, (*a*) $NaBH_4$, (*b*) H^+.

potassium hydroxide and the product acidified, an isomeric lactone (m. p. 71°, $[\alpha]_D$ +26°) is obtained, and this must be the 11-epimer (VI) of tetrahydroalantolactone. Confirmation is given by the fact that when either epimer (VII) or (VI) is heated for a short time with sodium methoxide, a mixture rich in the former is obtained, but when the heating is protracted the only product is the latter.

The behaviour described in the preceding paragraph is reminiscent of the chemistry of the desmotroposantonins.[14] Short treatment of the lactones with sodium methoxide will leave the lactone rings largely intact. Under these conditions, the lactone (VI) is epimerised at position 11 whilst the compound (VII) is unchanged. Lactone (VII), therefore, is more stable than (VI). Hence, according to the rules propounded by Chopra *et al.*,[4] the former (VII), which is a *cis*-fused lactone,[6] must have its 11-methyl group *cis* with respect to the 7-hydrogen atom, *i.e.*, there is a α-methyl group at position 11. We have confirmed this assignment by showing that tetrahydroalantolactone (VII) is stable to protracted heating with anhydrous potassium carbonate in boiling xylene. These are conditions which do not hydrolyse the lactone ring but invert position 11 when this is in the less stable configuration.[4,5,14]

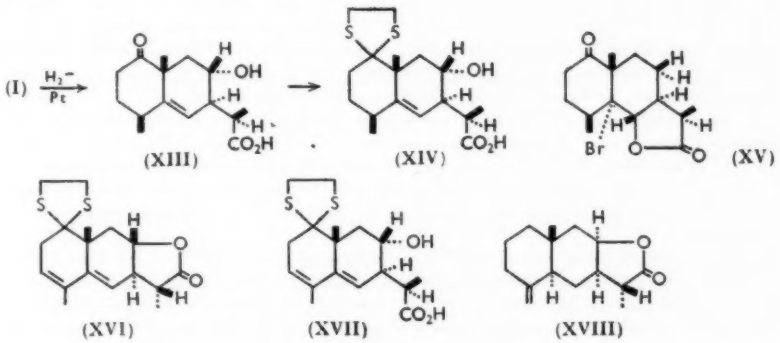
The acid or ester which is produced when the lactone (VII) is heated with potassium hydroxide or for long periods with methoxide will, however, have the less stable configuration at position 11, as shown in conformation (A), and will undergo inversion there [14] to afford the acid or ester which can adopt conformation (B). Relactonisation will then give the 11-epimer of tetrahydroalantolactone, namely, (VI).[13]



In the formation of 8α-hydroxy-4 : 5 : 11α(H)-eudesman-13-oic acid (V) from tetrahydroalantolactone (VII) (Scheme A), the intermediate ketone (VIII) is reduced when heated for several hours with sodium in propan-2-ol. These are conditions [13,14] which

[13] Asselineau, Bory, and Lederer, *Bull. Soc. chim. France*, 1955, 1524.
[14] Woodward and Yates, *Chem. and Ind.*, 1954, 1391; Chopra, Cocker, and Edward, *ibid.*, 1955, 41.

could lead to epimerisation at position 11 (cf. our preliminary communication [1]). We have now shown that no such epimerisation takes place in the sequence (VII) ⟶ (VIII) ⟶ (V), since it can be reversed. Thus when the methyl ester of acid (V) is oxidised, and the product reduced by sodium borohydride, tetrahydroalantolactone (VII) is obtained. In consequence, the acid (V) must have the configuration shown and its lactone,[6] m. p. 74—75°, $[\alpha]_D$ −29·3°, must have structure (IV) with an 11α-methyl group. This is the more unstable [4] of the two *trans*-fused lactones epimeric at position 11.[6] That this is the case is shown as follows. Reducing the keto-acid (VIII) with sodium and propan-2-ol gives the hydroxy-acid (V) and a lactone, m. p. 112—113° (lit.,[6] m. p. 108—109°, $[\alpha]_D$ −19·5°). This lactone can only have structure (IX), that of the 11-epimer of (IV), since the structures of three of the four possible lactones, namely, (IV), (VI), and (VII), have already been assigned. We need not consider the possible epimerisation at position 7 since the large group there must be equatorial. The fact that the new lactone is formed merely by acidification of the alkaline mixture after reduction of acid (VIII) shows that the new lactone is more stable than (IV), whose corresponding hydroxy-acid (V) is not lactonised under similar conditions [cf. the greater resistance to lactonisation of 11β(H)-santoninic acid than of santoninic acid; [15] at the same time one should distinguish the absolute stability of the hydroxy-acid at position 11 from its resistance to lactonisation].



(XIII) (XIV) (XV)

(XVI) (XVII) (XVIII)

The configuration at position 11 in ψ-santonin can now be assessed. The dithioketal (III) must, like its successor (IV) in Scheme A, have the more unstable 11α-methyl configuration. Obviously tetrahydro-ψ-santonic acid must have the configuration at position 11 shown in (IIb ≡ IIa) (we use this symbol to draw attention to the rotation about $C_{(7)}$–$C_{(11)}$, which is necessary to convert a linear into an angular lactone and *vice versa*). Hence ψ-santonin must have an 11β-methyl group.

We have made several attempts to determine the configuration at position 6 in ψ-santonin. These involved at one stage the removal of the keto-group *via* an ethylene dithioketal. Starting from 8α-hydroxy-1-oxo-4 : 11α(H)-eudesm-5-en-13-oic acid (XIII) (formerly called dihydro-ψ-santonin [4,16]) we prepared the dithioketal (XIV) which was not desulphurised by Raney nickel. The same dithioketal (XIV) was formed when the bromolactone (XV) [17] was treated with ethanedithiol and boron trifluoride, the thiol acting as a reducing agent.

ψ-Santonin itself afforded a dithioketal on treatment with ethanedithiol and toluene-*p*-sulphonic acid. By analogy with ψ-santonic acid [4] this product must have structure (XVI). Neither this nor the corresponding hydroxy-acid (XVII) could be desulphurised.

It is interesting that in one reduction of "helenin" over Raney nickel in methanol

[15] Miki, *J. Pharm. Soc. Japan*, 1955, **75**, 416.
[16] Clemo and Cocker, *J.*, 1946, 30.
[17] Cocker and Hornsley, *J.*, 1947, 1157.

dihydro*iso*alantolactone (XVIII) was obtained.[18] It showed maxima (KBr disc) at 1761 (butanolide), 1650 (isolated C=C), and 890 cm.$^{-1}$ (C=CH_2). The dihydro-compound is unchanged when refluxed for 24 hours with potassium carbonate in xylene, as would be expected since it is reduced to tetrahydroalantolactone (VII).

Experimental

Infrared spectra were measured with a Hilger 800 double-beam instrument. $[\alpha]_D$ refer to $CHCl_3$ solutions unless otherwise stated.

8α-*Hydroxy*-4 : 5 : 11α(H)-*eudesman*-13-*oic Acid* (V).—This acid, prepared from alantolactone by the method of Tsuda, Tanabe, Iwai, and Funakoshi,[6] had m. p. 185°, $[\alpha]_D^{17}$ +61·5° (*c* 0·67 in MeOH) {lit.,[6] m. p. 174°, $[\alpha]_D^{25}$ +66·6° (*c* 1·5 in EtOH)} (Found: C, 71·2; H, 9·9. Calc. for $C_{15}H_{26}O_3$: C, 70·8; H, 10·3%).

4 : 5α(H),11β(H)-*Eudesman*-8α : 13-*olide* 1-(*Ethylene Dithioketal*) (III).—A mixture of tetrahydro-ψ-santonic acid (0·5 g.)[4,5] and ethanedithiol (0·6 c.c.) was slowly treated with freshly distilled boron trifluoride–ether complex[8] (0·6 c.c.). After 3 hr. water was slowly added, then sodium carbonate to alkalinity, and the mixture was extracted with ether, from which a pale yellow gum was obtained. Trituration with methanol gave a solid which on crystallisation from ethanol afforded the *dithioketal* as prisms (50 mg.), m. p. 175—176°, $\nu_{max.}$ 1767 cm.$^{-1}$ (lactone) (Found: C, 62·9; H, 7·5. $C_{17}H_{26}O_2S_2$ requires C, 62·6; H, 8·0%).

8α-*Hydroxy*-4 : 5 : 11α(H)-*eudesman*-13-*oic Acid* (V).—A mixture of the above dithioketal (90 mg.), Raney nickel (1 g.), and dioxan (30 c.c.) was refluxed for 8 hr., then filtered and evaporated at 90° under reduced pressure. The residual glass was refluxed for 2 hr. with 10% aqueous potassium hydroxide (2 c.c.) in methanol (10 c.c.). Evaporation of the solvent and acidification of the residue gave a solid (30 mg.), m. p. 155—160°, which on crystallisation from ethanol afforded 8α-hydroxy-4 : 5 : 11α(H)-eudesman-13-oic acid (V), $[\alpha]_D^{17}$ +59·9° (*c* 0·11 in MeOH), m. p. 183°, alone or on admixture with a specimen prepared from alantolactone.

Attempted Conversion of Tetrahydroalantolactone (VII) *into its* 11-*Epimer* (VI).—The lactone (VII) (0·5 g.) in *m*-xylene (10 c.c.) was gently refluxed with freshly ignited potassium carbonate (0·5 g.) for 21 hr. The mixture was filtered whilst hot and the xylene was removed under reduced pressure, giving unchanged material, m. p. and mixed m. p. 148° (0·45 g. of material of m. p. 145—146°).

Conversion of 8α-*Hydroxy*-4 : 5 : 11α(H)-*eudesman*-13-*oic Acid* (V) *into Tetrahydroalantolactone* (VII).—The acid, m. p. 184° (10 mg.), was treated with excess of diazomethane in ether, and after 1 hr. the solvent was removed. The product, dissolved in acetic acid (2 c.c.), was set aside for 1·5 hr. with sodium dichromate (100 mg.) in acetic acid (4 c.c.). The excess of dichromate was decomposed with ethanol, and the solvents were removed under reduced pressure. The residue was extracted with ether, washed with water and sodium hydrogen carbonate solution, and dried. Removal of solvent gave a product which was dissolved in methanol (15 c.c.), mixed with potassium borohydride (50 mg.) in water (5 c.c.), and set aside for 14 hr. The solution was poured into water (40 c.c.), acidified with dilute acetic acid, saturated with ammonium sulphate, and extracted with ether. Removal of ether gave a residue which was heated at 100° for 3 min. and then crystallised from ethanol from which tetrahydroalantolactone (6 mg.), m. p. and mixed m. p. 140°, was obtained.

8α-*Hydroxy*-4 : 11α(H)-*eudesm*-5-*en*-13-*oic acid* 1-(*Ethylene Dithioketal*) (XIV).—Anhydrous hydrogen chloride was passed during 2 hr. into a mixture of 8α-hydroxy-1-oxo-4 : 11α(H)-eudesm-5-en-13-oic acid[15] (XIII) (0·6 g.) and ethanedithiol (1 c.c.). The product was diluted with ether, washed with water, and dried. Removal of the solvent gave the *dithioketal* (0·55 g.) as plates (from ethyl acetate–light petroleum), m. p. 180—181°, $[\alpha]_D^{19}$ +83·4° (*c* 0·82) (Found: C, 60·0; H, 7·3. $C_{17}H_{26}O_2S_2$ requires C, 59·6; H, 7·6%). The same product was obtained when boron trifluoride–ether was used as catalyst.

When the bromo-lactone[17] (XV) (0·55 g.) obtained from 8α-hydroxy-1-oxo-4 : 11α(H)-eudesm-5-en-13-oic acid was set aside for 24 hr. with ethanedithiol (1 c.c.) and boron trifluoride–ether (1 c.c.), the product was the same dithioketal (0·4 g.), m. p. and mixed m. p. 181°. No reaction took place between the bromo-lactone, ethanedithiol, and anhydrous hydrogen chloride.

11β(H)-*Eudesma*-3 : 5-*dien*-8α : 13-*olide* 1-(*Ethylene Dithioketal*) (XVI).—ψ-Santonin (1 g.),

[18] Cf. Ruzicka and van Melsen, *Helv. Chim. Acta*, 1931, **14**, 379; Ukita, Matsuda, and Nakazawa, *J. Pharm. Soc. Japan*, 1952, **72**, 796; cf. ref. 13.

ethanedithiol (1 c.c.), toluene-*p*-sulphonic acid (40 mg.), and benzene (50 c.c.) were refluxed with continuous removal of water in a Dean and Stark apparatus for 3 hr. The solution was shaken with water, the benzene layer dried, and the solvent was removed. The residue was crystallised from ethyl acetate, giving the *dithioketal* (0·28 g.) as rhombs, m. p. 185—186°, $[\alpha]_D^{19}$ +85·3° (*c* 1·3), $\nu_{max.}$ 1773 (γ-lactone), 1003 (*trans*-γ-lactone), and 860 cm.$^{-1}$ (trisubstituted double bond) (Found: C, 63·5; H, 7·2. $C_{17}H_{22}O_2S_2$ requires C, 63·3; H, 6·8%).

8α-*Hydroxy*-11α(H)-*eudesma*-3 : 5-*dien*-13-*oic Acid* 1-(*Ethylene Dithioketal*) (XVII).—The previous compound (0·15 g.) was refluxed for 1 hr. with potassium hydroxide (0·5 g.) and methanol (10 c.c.). Removal of solvent and acidification of the residue afforded the *hydroxy-acid* (0·1 g.), needles (from aqueous methanol), m. p. 186—187°, $[\alpha]_D^{20}$ +173·4° (*c* 0·47 in MeOH) (Found: C, 60·7; H, 7·35. $C_{17}H_{24}O_3S_2$ requires C, 60·0; H, 7·1%).

Hydrogenation of "Helenin."—"Helenin" (10 g.) in methanol (100 c.c.) was stirred in hydrogen for 14 hr. with Raney nickel (3 g.). Filtration and removal of solvent gave a residue which after two crystallisations from ethanol gave dihydro*iso*alantolactone (XVIII) (4 g.) as needles, m. p. 174° (Found: C, 76·75; H, 9·5. Calc. for $C_{15}H_{22}O_2$: C, 76·9; H, 9·5%).

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400. *The Determination of the Paramagnetic Susceptibility of Substances in Solution by Nuclear Magnetic Resonance.*

By D. F. EVANS.

The shifts of the proton resonance lines of *inert* reference molecules in solution caused by paramagnetic substances are accurately given by the theoretical espression $\Delta H/H = (2\pi/3)\Delta\kappa$ where $\Delta\kappa$ is the change in volume susceptibility. For aqueous solutions of paramagnetic substances, about 2% of t-butyl alcohol is incorporated, and an aqueous solution of t-butyl alcohol of the same concentration is used as an external reference. Values obtained for the susceptibility of a variety of paramagnetic molecules are in satisfactory agreement with those in the literature. Less than 0·03 ml. of a dilute solution can be studied.

THE position of a line in the proton resonance spectrum of a molecule depends on the bulk susceptibility of the medium in which the molecule is situated. For an inert substance (dioxan) in aqueous solution, the shifts caused by paramagnetic ions are given [1] by the theoretical expression [2]

$$\Delta H/H = (2\pi/3)\Delta\kappa \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $\Delta\kappa$ is the change in volume susceptibility. This is consistent with some earlier work of Phillips, Looney, and Ikeda [3] on the nuclear magnetic resonance spectra of alcohols containing paramagnetic ions, and is in contrast with measurements on mixtures of diamagnetic liquids [4] where higher values of the numerical factor (~2·60) were obtained. A simple method of measuring the paramagnetic susceptibilities of substances in dilute solution is therefore available. Bothner-By and Glick [4] have suggested the use of eqn. (1) with a numerical factor of 2·60 for measuring the susceptibilities of *diamagnetic* substances, but the presence of an empirical factor of doubtful constancy seems to detract from the utility of this method.

For aqueous solutions of paramagnetic substances about 2% of t-butyl alcohol is

[1] Evans, *Proc. Chem. Soc.*, 1958, 115.
[2] Dickinson, *Phys. Rev.*, 1951, **81**, 717.
[3] Phillips, Looney, and Ikeda, *J. Chem. Phys.*, 1957, **27**, 1435.
[4] Bothner-By and Glick, *J. Chem. Phys.*, 1957, **26**, 1647.

XUM

incorporated as an inert reference substance, and a capillary containing the same concentration of t-butyl alcohol in water is also placed in the nuclear magnetic resonance tube which is spun during the measurement. (The change in the susceptibility of the dissolved compound caused by the t-butyl alcohol will normally be completely negligible.) Two resonance lines will normally be obtained from the methyl protons of the t-butyl alcohol in the two solutions owing to the difference in their volume susceptibilities, with the line from the more paramagnetic solution lying at higher frequencies. The mass susceptibility, χ, of the dissolved substance is then given by the expression

$$\chi = \frac{3\Delta f}{2\pi f m} + \chi_0 + \frac{\chi_0(d_0 - d_s)}{m} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where Δf is the frequency separation between the two lines in cycles/sec., f is the frequency at which the proton resonances are being studied, in cycles/sec., m is the mass of substance contained in 1 ml. of solution, χ_0 is the mass susceptibility of the solvent ($-0{\cdot}72 \times 10^{-6}$ for dilute t-butyl alcohol solutions), d_0 is the density of the solvent and d_s that of the solution. For highly paramagnetic substances the last term can often be neglected without serious error (2% for $NiCl_2$ solutions). Acetone or dioxan can also be used in place of t-butyl alcohol or, for non-aqueous solutions, cyclohexane or tetramethylsilane.[5] Alternatively a resonance line of the organic solvent itself can be used as a reference, provided there is no interaction with the solute.

Results obtained for various paramagnetic substances are given in the Table, and are in satisfactory agreement with the literature values.

Mass-susceptibilities in solution at $20° \pm 1°$.

Substance	Concn. (M) *	$10^6\chi$ calc. from eqn. (2)	$10^6\chi$ (lit.)
$NiCl_2$ †	0·162	$34{\cdot}00 \pm 0{\cdot}2$	$34{\cdot}20 \pm 0{\cdot}1$ [a]
,,	0·081	$34{\cdot}14 \pm 0{\cdot}3$	$34{\cdot}20 \pm 0{\cdot}1$ [a]
$CuSO_4$	0·0788	9·6	10·1 [b]
$K_3Fe(CN)_6$	0·061	7·67	8·24,[c] 6·32 [d]
$NH_4[Cr(CNS)_4(NH_3)_2]$	0·0152	18·6	17·4 [e]
$Ph_3N{\cdot}N(Picryl)$·	0·0475 §	2·46	2·07,[f] 2·75,[g] 2·70 [h]

* In 2% aqueous t-butyl alcohol, except for diphenylpicrylhydrazyl § which is in 10% cyclohexane (reference)–90% benzene (v/v). † At $20{\cdot}0° \pm 0{\cdot}2°$.

[a] Selwood, "Magnetochemistry," Interscience, New York, 1956, p. 25. [b] Amiel, *Compt. rend.*, 1941, **213**, 240. [c] Sloth and Garner, *J. Chem. Phys.*, 1954, **22**, 2064. [d] Gray and Birse, *J.*, 1914, **105**, 2707. [e] Berkmann and Zacker, *Z. phys. Chem.*, 1926, **124**, 318 (solid; temp. not stated). [f] Turkevich and Selwood, *J. Amer. Chem. Soc.*, 1941, **63**, 1077 (solid). [g] Müller, Müller-Rodloff, and Bunge, *Annalen*, 1935, **520**, 235 (benzene solution). [h] Ref. *g* (solid).

Care should be taken that the concentration of solute is not too high, otherwise the line from the solution will be too broad. The relative magnitude of this effect varies considerably. Thus it is much smaller for nickel or cobaltous complexes than for cupric or chromic complexes (cf. Conger and Selwood [6]).

One particular advantage of the method described above is that only about 0·2 ml. of solution is required. Less than 0·03 ml. of solution can be measured if the concentration of the reference substance is increased somewhat, and the solution to be examined is placed in a narrow capillary tube. In this case the *reference* solution is contained in the main nuclear magnetic resonance tube which, for small frequency shifts, should preferably be of narrow bore to avoid large differences in the intensities of the two resonance lines. The contribution to the measured susceptibility caused by additional diamagnetic solutes (including ligand molecules) can be eliminated by including an equal concentration in the reference solution.

[5] Tiers, *J. Phys. Chem.*, 1958, **62**, 1151.
[6] Conger and Selwood, *J. Chem. Phys.*, 1952, **20**, 383.

Experimental

Measurements were made at 40 Mc./sec. on a Varian V4300B spectrometer. 5-mm. o.d. (3·5-mm. i.d.) spinning sample tubes were used, with loose thin-walled capillary tubes ~2·5 mm. o.d. Precision-bore tubes, with the capillary mounted centrally,[7] were not available but would probably prove advantageous. Line separations were measured by the conventional side-band technique, with a Muirhead decade oscillator. The 50 cycles/sec. mains frequency was also used as a more precise standard with the nickel chloride solutions. The accuracy of this frequency during the time measurements were made was kindly confirmed by an engineer at the local Power Station.

Nickel chloride solutions (from " AnalaR " nickel chloride) were analysed for nickel by precipitation with dimethylglyoxime. $NH_4[Cr(CNS)_4(NH_3)_2],H_2O$ was once recrystallised from water. αα-Diphenyl-β-picrylhydrazyl was prepared as described by Goldschmidt,[8] and twice recrystallized from carbon disulphide. " AnalaR " copper sulphate pentahydrate and " AnalaR " potassium ferricyanide were used directly.

The author thanks Dr. L. Pratt for helpful discussions.

Inorganic Chemistry Research Laboratories,
Imperial College, London, S.W.7. [*Received, February 10th*, 1959.

[7] Zimmerman and Foster, *J. Phys. Chem.*, 1957, **61**, 282.
[8] Goldschmidt, *Ber.*, 1922, **55**, 628.

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401. *Infrared Spectra of Natural Products. Part XII.* Triterpenoid and Diterpenoid Carboxylic Acids.*

By A. R. H. Cole and A. J. Michell.

The infrared spectra of a group of triterpenoid and diterpenoid carboxylic acids have been measured in carbon tetrachloride and chloroform and a few in carbon disulphide and dioxan solutions. Hydroxyl and carbonyl frequencies are given for the monomeric and the dimeric acids, and the distribution of the acids between monomer and dimer is studied in the different solvents. Most of the acids exist as monomer in dioxan, predominantly as monomer in chloroform, and predominantly as dimer in carbon disulphide and tetrachloride. In the carbonyl region the change from mostly dimer (~1695 cm.$^{-1}$) in carbon tetrachloride to mostly monomer (~1735 cm.$^{-1}$) in chloroform can be useful in identifying an unknown compound as an acid since all other types of carbonyl function absorb at lower frequencies in chloroform. Dicarboxylic acids and polyhydroxy-acids might exist as dimers in all solvents if the substituent groups are favourably oriented for the formation of more than one hydrogen-bond system.

Carboxylic acids in the polyterpenoid field can often be isolated and purified more readily than alcohols and hydrocarbons but, in general, they are not so convenient for infrared structural analysis. They form very strong intermolecular hydrogen-bonds and hence are usually sparingly soluble in the non-polar solvents which are best for infrared work, and their spectra [1-4] are complicated by the presence of various proportions of dimeric and monomeric molecules. It is usual to overcome these difficulties in degradative work by converting acids into methyl esters, but, as part of a programme based on correlations of

* Part XI, *J.*, 1959, 1224.

[1] Davies and Sutherland, *J. Chem. Phys.*, 1938, **6**, 755.
[2] Shreve, Heether, Knight, and Swern, *Analyt. Chem.*, 1950, **22**, 1948.
[3] Flett, *J.*, 1951, 962.
[4] Hadži and Sheppard, *Proc. Roy. Soc.*, 1953, *A*, **216**, 274; Harris and Hobbs, *J. Amer. Chem. Soc.*, 1954, **76**, 1419; Bratož, Hadži, and Sheppard, *Spectrochim. Acta*, 1956, **8**, 249; Wenograd and Spurr, *J. Amer. Chem. Soc.*, 1957, **79**, 5844.

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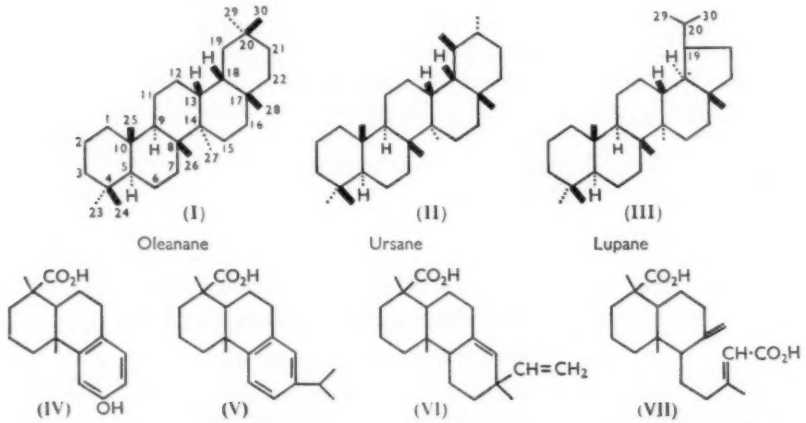
triterpenoid structures with infrared spectra, we have investigated the spectra of dilute solutions of the acids themselves in a number of solvents.[5]

Experimental.—The experimental conditions were as in Parts V and VIII of this series.[6] Cells of 10 mm. path length were often necessary because of the low solubility of some of the compounds.

Results and Discussion.—Most of the acids studied in this work are triterpenoids based on oleanane (I), ursane (II), or lupane (III). Of the others one is a degradation product of lanosterol, one is coprostan-27-oic acid,[7] and four [(IV)—(VII)] are diterpenoids. Propionic and benzoic acid are included for comparison.



Their hydroxyl and carbonyl stretching frequencies in carbon tetrachloride and chloroform solutions are given in Table 1, where maximum values of the apparent molar extinction coefficients are given for those compounds soluble enough for quantitative measurements.

Hydroxyl absorption. Carboxylic acids exist in these solvents in varying proportions of monomer and dimer (see below). The carboxyl-hydroxyl absorption of the monomer (in CCl_4) occurs at about 3535 cm.$^{-1}$ and is easily distinguished from alcoholic-hydroxyl absorption near 3630 cm.$^{-1}$, while that of the dimer is extremely broad and underlies the C–H stretching absorption at much lower frequencies[4] (Fig. 1). Alcoholic-hydroxyl frequencies are lowered by about 10 cm.$^{-1}$ in chloroform while the monomer carboxyl-hydroxyl frequency falls by 15—25 cm.$^{-1}$. Absorption of chloroform interferes with hydroxyl measurements on the dimer.

The absorption frequency of the equatorial secondary 3-hydroxyl group (3630 cm.$^{-1}$) for a number of the compounds is consistent with previous measurements on triterpenoid alcohols,[8,9] while the high frequency for β-boswellic acid (3638 cm.$^{-1}$) shows that this hydroxyl group is axial. The absence of absorption due to intramolecular hydrogen-bonding[10] means that the 4-carboxylic group is also axial, thus establishing the structure

[5] Michell, Thesis, W. Australia, 1956.
[6] Cole and Thornton, *J.*, 1956, 1007; Cole and Willix, *J.*, 1959, 1212.
[7] Bridgwater and Haslewood, *Biochem. J.*, 1952, **52**, 588.
[8] Allsop, Cole, White, and Willix, *J.*, 1956, 4868.
[9] Cole, Müller, Thornton, and Willix, *J.*, 1959, 1218.
[10] Cole and Müller, *J.*, 1959, 1224.

TABLE 1. *Hydroxyl and carbonyl frequencies (cm.$^{-1}$) of carboxylic acids in various solvents. Apparent molar extinction coefficients are given in parentheses.*

TABLE 1. *Hydroxyl and carbonyl frequencies (cm.$^{-1}$) of carboxylic acids in various solvents. Apparent molar extinction coefficients are given in parentheses.*

Compound	Alcoholic OH		Carboxyl OH		Carbonyl						Dioxan	
					CCl_4		$CHCl_3$		CS_2			
	CCl_4	$CHCl_3$	CCl_4	$CHCl_3$	Monomer	Dimer	Monomer	Dimer	Monomer	Dimer	Monomer	Complex
3β-Hydroxyolean-12-en-28-oic acid (oleanolic acid)	3630(60)	3621(80)	3537(45)	3512(65)	1744(140)	1696(590)	1734(225)	1696(190)	1743	1694	1727	1644
3β-Hydroxyolean-19-en-28-oic acid (morolic acid)	3630	3621(90)	3532	3507(65)	1743(275)	1696(490)	1734(290)	1696(135)				
3β-Hydroxyolean-13(18)-en-28-oic acid (δ-oleanolic acid)	3629(50)	3617(80)	3530(30)	3515(55)	1742(150)	1693(380)	1732(255)	1693(220)				
3β-Hydroxyurs-12-en-28-oic acid (ursolic acid)					1742	1691	1731	1694				
3α-Hydroxyurs-12-en-24-oic acid (β-boswellic acid)	3638[a](70)	3631[a](65)	3524(35)	3509(45)	1737(165)	1694(455)	1731(345)	1694(145)	1736(95)	1692(585)	1718	1650
Olean-12-en-30-oic acid (deoxydeoxoglycyrrhetic acid)			3535(30)	3518(70)	1747(160)	1699(535)	1738(400)	1698(275)				
3-Oxolupan-28-oic acid (dihydrobetulonic acid)			3528(35)	3513(50)	1742(220)	1697[b]	1737(355)	1699[c](570)			1726	1644
3β-Hydroxyoleana-11:13(18)-dien-28-oic acid (dehydrooleanolic acid)	3630	3615	3531	3508	1743	1695	1736	1695				
3β:23-Dihydroxyolean-12-en-28-oic acid (hederagenin)	*	*	*	*	*	*	1733	1697 1682				
3β-Acetoxyolean-12-en-28-oic acid (acetyloleanolic acid)			3534(25)	3520(40)	1745[b]	1696	1731[b]	1695[b]	1745[b]	1696(575)	1731[b]	1637
3β-Acetoxy-18α-olean-12-en-28-oic acid (acetyl-18-*iso*-oleanolic acid)					1752[b]	1700	1741[b]	1700[b]				
3β-Acetoxy-23-oxo-olean-12-en-28-oic acid (gypsogenin acetate)			3532(15)	3515(50)	1747[b]	1697(565)	—[c] (1730)	1698				
3β-Acetoxylup-20(29)-en-28-oic acid (acetylbetulic acid)			3533(35)	3516(50)	1745[b]	1694	1733[b]	1695[b]				
3β-Hydroxyurs-12-ene-27:28-dioic acid (quinovic acid)	*	*	*	*	No abs.	1693[b] 1678	No abs.	1693[b] 1678				
3β-Hydroxy-(25–27)-trisnorlanost-8-en-24-oic acid					*	*	1745	1710[b]				
Coprostan-27-oic acid (coprostanic acid)			3530(40)	3518(45)	1755	1708	1742(310)	1706(220)				
Dehydroabietic acid			3537(50)	3522(55)	1743(175)	1695(565)	1734(425)	1695(385)				
Podocarpic acid	3618[d]	3603[d]	3528	3514	1743	1696	1735	1696				
Dextropimaric acid			3534(40)	3512(50)	1742(150)	1696(575)	1732(250)	1694(180)				
Agathenedicarboxylic acid			*	3512	1740	1693	1725(450)	1693(332)				
Propionic acid			3535(10)		1760(71)	1716(600)	1747(303)	1715(223)	1760(67)	1714(595)	1739	1640
Benzoic acid			3535(20)		1742(85)	1697(710)	1732(360)	1697(350)	1741(110)	1697(590)	1723	1636

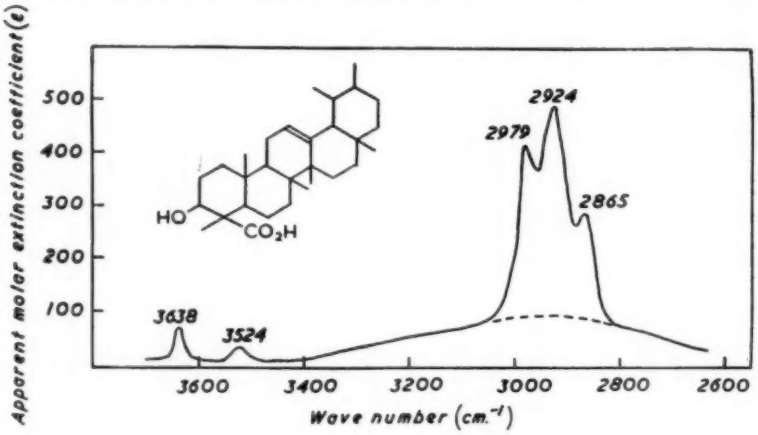
* Measurement impossible because of low solubility.

[a] Axial hydroxyl. [b] Partially resolved shoulder on side of stronger band. [c] Indistinguishable from acetate-carbonyl absorption (maximum in parentheses). [d] Phenolic OH. [e] Includes 3-ketone absorption.

of this region of β-boswellic acid [5] in agreement with the chemical evidence of Beton, Halsall, and Jones.[11]

The phenolic-hydroxyl frequency of podocarpic acid (3618 cm.$^{-1}$ in CCl_4) is also readily distinguished from those of the secondary alcoholic compounds. The apparent molar extinction coefficients of the hydroxyl absorption may be inaccurate because of low solubility, but they indicate the order of magnitude of the intensities, and the increase in the intensity of the monomeric carboxyl-hydroxyl band on change from carbon tetrachloride to chloroform is consistent with the measurements in the carbonyl region (see

FIG. 1. *Spectrum of β-boswellic acid in the hydroxyl and* C–H *stretching regions* (CCl_4 *solution*).



below). However, the proportions of monomer and dimer are not identical for the two regions since the solutions used for the hydroxyl absorption were, of necessity, much more concentrated.

C–H *Stretching absorption.* All terpenoids show strong absorption near 2900 cm.$^{-1}$ due to the stretching vibrations of the alphatic C–H bonds (Fig. 1). However, this absorption is not very sensitive to small changes in molecular structure and provides very little useful information. Ethylenic C–H stretching absorption on the high-frequency side of the main band is often useful in identifying unsaturated centres, but the absorption is relatively weak and is obscured by the broad hydrogen-bonded dimer absorption in the spectra of the acids. Even the vinylidene band at 3070 cm.$^{-1}$ ($\varepsilon \sim 40$) which is usually easy to find was not visible in the spectrum of dextropimaric acid. The spectra of the acids were all measured in this region, but since no new information was obtained they will not be considered further.

Carbonyl absorption. The physical state in which carboxylic acids are examined has a direct effect on the carbonyl frequency. The carbonyl bands of monomer and dimer are easily resolved (Table 1) and their intensity ratio indicates the degree of association under different conditions.* Table 1 shows that the monomer carbonyl frequency measured in chloroform is approximately 10 cm.$^{-1}$ lower than in carbon tetrachloride and carbon disulphide, while that of the dimer is the same for all solvents. In dioxan the acids are

* A broad band centred near 1714 cm.$^{-1}$ reported by Cole and Thornton [6] for a few triterpenoid acids in chloroform is now known to be due to hydrogen-bonding to ethanol (0·5%) present in the solvent as stabiliser. Most types of carbonyl group can be studied in the presence of the ethanol, but for the carboxylic acids with their much greater tendency to form hydrogen-bonds it must be removed. For the present work this was done with silica gel.[12]

[11] Beton, Halsall, and Jones, *J.*, 1956, 2904.
[12] Cole, *Fortschr. Chem. org. Naturstoffe*, 1956, **13**, 17.

mainly monomeric (see below) and the carbonyl frequency is 7—13 cm.$^{-1}$ lower than in chloroform. These (monomer) solvent effects are similar to those reported for simpler carbonyl compounds,[13] although here the greater lowering in dioxan should be noted. The absence of a differential solvent shift in the case of the dimer must be due to the difficulty of approach of solvent molecules to the " internal " carbonyl groups, an effect similar to that reported by Bayliss, Cole, and Little [13] for the C–C bond of acetonitrile in a variety of solvents.

There is a marked increase in the proportion of monomer to dimer in changing from carbon tetrachloride to chloroform. This is in the expected direction since the polar solvent would stabilise the more polar monomeric form. The proportion of monomer is about the same in carbon disulphide as in carbon tetrachloride, while in dioxan the acids

FIG. 2. *Carbonyl region of the spectrum of β-boswellic acid in CCl_4–$CHCl_3$ mixtures (see Table 2).*

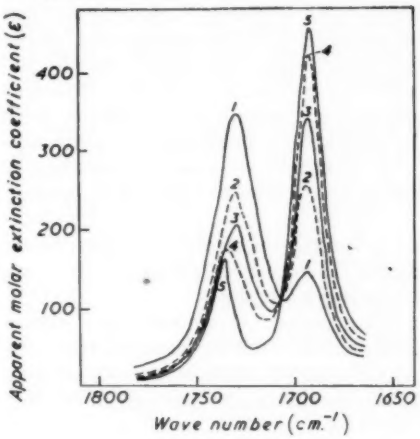
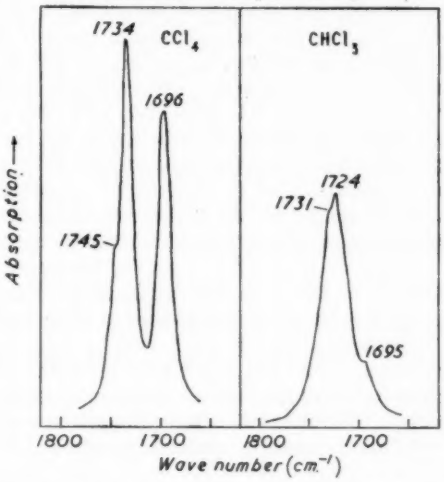


FIG. 3. *Carbonyl region of the spectrum of acetyloleanolic acid in CCl_4 and $CHCl_3$.*



exist almost completely as monomer.[3] However, in the latter solvent there is some tendency to form a hydrogen-bond to a dioxan-oxygen, as shown by the small broad band near 1640—1650 cm.$^{-1}$.

The change from predominantly dimeric in carbon tetrachloride to monomeric in chloroform was followed quantitatively for β-boswellic acid in mixtures of the two solvents (Table 2 and Fig. 2). The isosbestic point for the system is at 1708 cm.$^{-1}$ (ε 110). These curves also show clearly the constant frequency of the dimer, the solvent shift of the monomer, and the broader shape of the bands in chloroform.

TABLE 2. *Carbonyl frequencies (cm.$^{-1}$), and apparent molar extinction coefficients (in parentheses), for β-boswellic acid in carbon tetrachloride–chloroform mixtures (see Fig. 2).*

Curve no. (Fig. 2)	Mole fractions CCl_4	Mole fractions $CHCl_3$	Monomer	Dimer	Curve no. (Fig. 2)	Mole fractions CCl_4	Mole fractions $CHCl_3$	Monomer	Dimer
1	1	0	1737(165)	1694(455)	4	0·16	0·84	1731(250)	1694(255)
2	0·75	0·25	1736(170)	1694(415)	5	0	1	1730(345)	1694(145)
3	0·52	0·48	1731(190)	1694(340)					

In structural analysis the monomer–dimer change can be useful in showing that carbonyl absorption is due to the presence of a carboxyl group, since the more intense part of the absorption appears to move to a higher frequency in chloroform whereas other types

[13] Josien and Lascombe, *Compt. rend.*, 1954, **238**, 2414; Bayliss, Cole, and Little, *Austral. J. Chem.*, 1955, **8**, 26.

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of carbonyl function move to lower frequencies. It can also be helpful in separating overlapping absorption if quantitative measurements are not used to determine the number of carbonyl groups in a compound.[14] For example, in the spectrum of acetyloleanolic acid (Fig. 3) the acetate-carbonyl band lies between that of the monomer and the dimer and, in chloroform, the slightly resolved shoulders at 1731 (monomer) and 1695 cm.$^{-1}$ (dimer) could easily be missed, especially if a sodium chloride prism is used, whereas the carbon tetrachloride solution shows conclusively that two types of carbonyl function are present.

The fact that the degree of association is approximately equal in carbon tetrachloride and carbon disulphide is important since the former solvent is the best (most transparent) for infrared work between 2·5 and 8 μ while the latter is the best liquid for the range 8—15 μ. It is thus possible to obtain the complete spectrum in solution between 2·5 and 15 μ with the acid in approximately the same state of association.

The low solubilities of hederagenin and quinovic acid, which prevented measurements in the hydroxyl region in either solvent and in the carbonyl region of the former in carbon tetrachloride, can be explained in terms of hydrogen-bond formation. Hederagenin has the possibility of dimerisation involving carboxyl–carboxyl, carboxyl–alcohol, or alcohol–alcohol hydrogen-bonds. The existence of the first two of these types is indicated by the two dimer carboxyl bands (1697, 1682 cm.$^{-1}$) in chloroform solution. Of these, that with the higher frequency must belong to the carboxyl–carboxyl system since it occurs in all the other acids, and the band at 1682 cm.$^{-1}$ to the carboxyl–alcohol bond. The intensity and appearance of the hydroxyl absorption of the monohydroxy-acids and absence of such low-frequency carbonyl absorption shows that they have none of this type of bonding in solution, although it could occur in the solids.

Quinovic acid exhibits similar absorption, but is sufficiently soluble in carbon tetrachloride to allow qualitative carbonyl measurements. The spectrum shows that it exists completely in the hydrogen-bonded form even in chloroform solution.

Trisnorlanostenolic acid, with a primary carboxyl group, also forms very strong hydrogen-bonds and is not soluble enough in carbon tetrachloride for measurement. In chloroform, its monomeric carbonyl absorption is very broad, probably because of easy access of solvent molecules to the primary group, and the dimer absorption at 1710 cm.$^{-1}$ could not be properly resolved from it.

TABLE 3. *Miscellaneous absorption frequencies* (*cm.*$^{-1}$).

In CCl_4		In $CHCl_3$	In CCl_4		In $CHCl_3$
	Acetate-carbonyl groups			*3-Ketones*	
1734	Acetyloleanolic acid	1724	1707	Dihydrobetulonic acid	1699 [a]
1734	Acetyl-18-*iso*oleanolic acid	1725	1707	Methyl dihydrobetulonate	
1737	Gypsogenin acetate	1730		*Vinylidene* C=C *frequency*	
1735	Acetylbetulic acid	1723	1643	Acetylbetulic acid	1642
			1644	Agathenedicarboxylic acid	1644

[a] Indistinguishable from dimeric acid absorption.

A number of miscellaneous band frequencies which were recorded are given in Table 3. They are consistent with those previously reported for similar triterpenoids.[6,12]

Other characteristic carboxylic acid absorption bands. (i) Near 1400 cm.$^{-1}$. Flett [3] and Hadži and Sheppard [4] have described a band between 1395 and 1440 cm.$^{-1}$ in a large number of acids. This is a region of strong methyl and methylene absorption in terpenoid and steroid spectra, and although bands undoubtedly associated with the carboxyl group were found for some of the present compounds (coprostanic acid 1418 cm.$^{-1}$, β-boswellic acid 1410 cm.$^{-1}$) it does not appear to be a useful region for structural information in this field.

(ii) Near 1250 cm.$^{-1}$. A band near 1250 cm.$^{-1}$ appeared in the spectra of all the acids examined by Flett,[3] and Shreve *et al.*[2] and Freeman [15] described a doublet near 1280 and

[14] Ramsay, *J. Amer. Chem. Soc.*, 1952, **74**, 72; Jones, Ramsay, Keir, and Dobriner, *ibid.*, p. 80.
[15] Freeman *ibid.*, p. 2523.

1240 cm.$^{-1}$. Of the acids in the present work which were studied beyond the calcium fluoride region, most show this doublet strongly, with some variation in the intensity ratio of the peaks (Table 4).

TABLE 4. *Absorption frequencies (cm.$^{-1}$) near 1250 cm.$^{-1}$ Apparent molar extinction coefficients (CS_2 solutions) are given for the more soluble acids.*

Oleanolic acid	1270, 1237	Acetyloleanolic acid	1270(200), 1241 [b]
β-Boswellic acid	1262(175), 1240 [a]	Coprostanic acid	1288, 1236
δ-Oleanolic acid	1266, 1228	Propionic acid	1280(95), 1234(135)
Dihydrobetulonic acid	1273(330), 1240(525)	Benzoic acid	1283(370)

[a] Partially resolved shoulder. [b] Mostly acetate absorption.

(iii) O–H Deformation absorption. A band near 935 cm.$^{-1}$ has been assigned (Hadži and Sheppard [4]) to the OH out-of-plane deformation mode of the dimeric acids. This appeared as a broad, fairly intense band in the spectra of benzoic (933 cm.$^{-1}$), propionic (932 cm.$^{-1}$), β-boswellic (946 cm.$^{-1}$), and coprostanic acid (984 cm.$^{-1}$) in this work. For some of the other acids, particularly those with tertiary carboxyl groups and those containing other oxygenated groups with fairly intense bands in the range 900—1100 cm.$^{-1}$ it did not stand out and might not always be of use in structure determinations.

The authors are grateful to Professor D. H. R. Barton, F.R.S., who supplied most of the compounds. The infrared spectrometer was purchased through a generous grant from the Nuffield Foundation.

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402. *Spectra of Arylammonium Ions.*

By I. G. Ross and M. LORRAINE TONNET.

The intensities of weak electronic absorption bands in solutions of arylammonium ions, including tri-*N*-methylanilinium ion, are essentially insensitive to the ionic strength of the solution and to the nature of the solvent. These intensities remain difficult to reconcile with present theory.

IT has long been recognized [1,2] (sometimes under the title of " Waterman's effect ") that the electronic spectra of aromatic and heteroaromatic molecules are virtually unaffected by the attachment of an $-NH_3^+$ group, whereas in the corresponding amines the spectra are shifted towards the red and greatly intensified. Sklar [3] accordingly concluded that purely inductive, as opposed to mesomeric effects could be neglected in the theory of substitutional spectral shifts.

It is not surprising that there should be a marked difference in effectiveness between the two types of perturbation,[4] but it has proved difficult to understand why $-NH_3^+$ groups should have no significant effect. This is especially so in the case of the 2600 Å system of benzene and the 3200 Å system of naphthalene, which are intrinsically very weak and depend upon perturbations, ordinarily provided by certain vibrations, for their intensities. The perturbation provided by a whole electronic charge close to the ring should be large, and in reaction kinetics it shows up clearly in the strong *meta*-directing properties of the $-NH_3^+$ group.[5] Consequently, it is hardly surprising that calculations [by Prof. D. P. Craig and one of us (I. G. R.); unpublished because so unsuccessful] of the intensity of the 2600 Å system of $C_6H_5{\cdot}NH_3^+$ consistently predict large enhancements

[1] Ramart-Lucas and Wohl, *Compt. rend.*, 1933, **196**, 1804.
[2] Harberts, Heertjes, van der Hulst, and Waterman, *Bull. Soc. chim. France*, 1936, **3**, 643.
[3] Sklar, *J. Chem. Phys.*, 1939, **7**, 984.
[4] Goodman, Ross, and Shull, *ibid.*, 1957, **26**, 474.
[5] Ingold, *Chem. Rev.*, 1934, **15**, 225.

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relative to benzene; yet the standard types of molecular wave-function are quite well suited for calculations of the π-electron polarizability of benzene [6,7]—a closely related quantity. The model used in the calculations on the anilinium ion was a benzene ring with a charge $+e$ located at the observed C–N bond distance, but it was consistently found that even a charge as small as $0{\cdot}1e$ should measurably alter the spectrum (whose intensification is roughly proportional to the square of the perturbing charge).

This disagreement between calculation and experiment caused us to reconsider the validity of the model. A free-ion spectrum cannot be studied alone; the amines are weak bases and their spectra have all been recorded in aqueous acid solutions of strength 0·01M or more. It seemed possible, therefore, that the full effect of a positively charged substituent might be heavily reduced by an oppositely charged ionic atmosphere or by solvation of the $-NH_3^+$ group. If so, then the intensity should vary with ionic strength, nature of the cations present, and polarity of the solvent.

Spectra in the literature are insufficient to resolve this question, so we examined closely those of anilines and naphthylamines in a variety of solvents, concentrating on the two band systems cited above since they, especially, should be sensitive to changes in molecular environment. As a preliminary, the spectrum of benzene was investigated in water, 4M-hydrochloric acid, and 4M-sodium chloride and found to be identical in all three media.

The substances studied (references are to previous measurements of their acid solution spectra) were aniline,[2,8,9] *N*-methylaniline, di-*N*-methylaniline,[8,10] tri-*N*-methylanilinium chloride, and 1-[9] and 2-naphthylamine.[9,10] The ions added were H^+, K^+, Na^+, Li^+, Cl^-, ClO_4^-, SO_4^{2-}, selected because their absorptions are not too intense in the regions of interest. Representative spectra are shown in the Figure along with the molar extinction coefficient, ε, of the strongest peak and the f value (omitted for the naphthylamines because a stronger transition underlies the 3200 Å system).

The spectra are clearly insensitive to environment, the small variation observed being not far beyond the accuracy of the measurements (determined largely by purity), and in any event nowhere exceeding 5%. Particularly significant are the results on the previously unstudied quaternary salt, tri-*N*-methylanilinium chloride, which is stable in neutral solutions. Its spectrum is virtually the same in water, aqueous solutions of high ionic strength, methanol, and hexane containing just enough methanol to allow it to form a 0·002M-solution.

Among the other amines, a close search was made for specific ionic interactions. The most marked were in acid–salt mixtures of relatively low H^+ concentration and could safely be attributed to activity effects and the presence of traces of free base. At acid concentrations above 0·1M, variations of intensity did not exceed 3%, generally increasing slightly with increasing salt molarity up to 4M. At constant molarity, substitution of ClO_4^- for Cl^- had no effect, and SO_4^{2-} (from observations on 1-naphthylamine only) caused a slight decrease in intensity. Partial replacement of H^+ by alkali-metal ions only very slightly (<3%) altered the intensity.

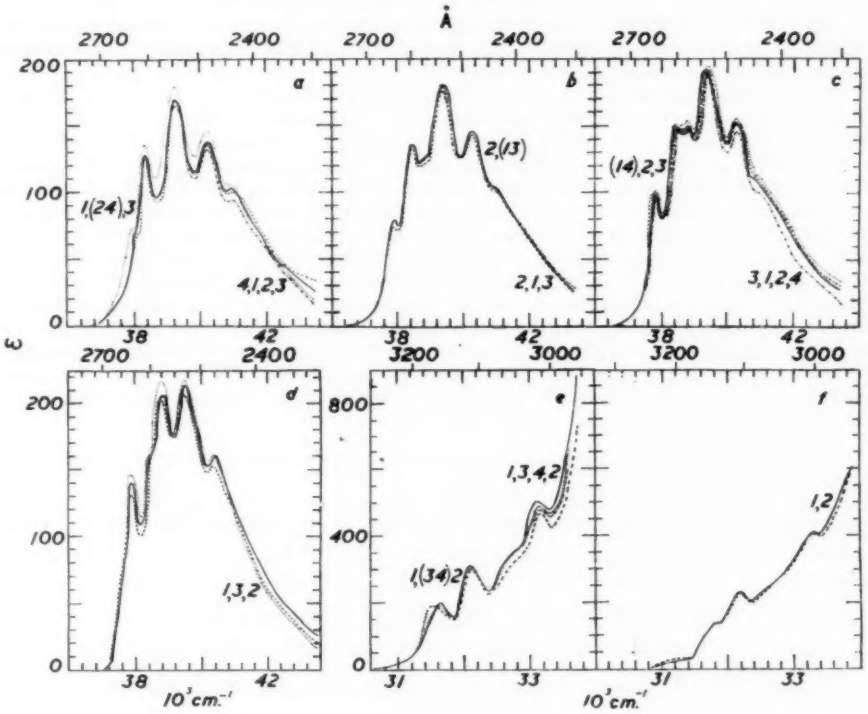
N-Methylation of anilinium ion increased the intensity by approximately 6% for each methyl group added. Some intensification is expected as the mass of the substituent is increased (the f value for hexachlorobenzene is twice that of benzene), but the methylation effect is probably partly due to interaction of the methyl groups with the ring (*e.g.*, *via* hyperconjugation).[11]

This work thus emphasizes the generality of the original experimental result; the intensities of the spectra of arylammonium ions persistently remain unexpectedly low. Polysubstitution also has no demonstrable effect, as is shown by earlier work on the

[6] Bolton, *Trans. Faraday Soc.*, 1954, **50**, 1265.
[7] Ross and Yates, unpublished calculations.
[8] Wohl, *Bull. Soc. chim. France*, 1939, **6**, 1312.
[9] Ramart-Lucas, *ibid.*, 1950, **17**, 262.
[10] Moede and Curran, *J. Amer. Chem. Soc.*, 1949, **71**, 852.
[11] Jones, *ibid.*, 1945, **67**, 2127.

phenylenediamines [12-15] (which, for the *meta*-compound, we checked). We are forced to assume then that the rôle of the solvent, whose presence is virtually unavoidable, is relegated to that of a polarizable medium surrounding the absorbing species, but we feel it must be necessary to take into account its bulk dielectric properties, as well probably

Absorption spectra of arylammonium ions.



Values of $\varepsilon_{max.}$ in parentheses.

(*a*) Aniline. (1) 10N-HCl (181 at 39,300 cm.$^{-1}$); (2) 1N-HCl (169; $f = 0{\cdot}0023$); (3) 0·1N-HCl (166); (4) 0·1N-HCl (170).
(*b*) *N*-Methylaniline. (1) 1N-HCl (181 at 39,450 cm.$^{-1}$; $f = 0{\cdot}0026$); (2) 0·1N-HCl (177); (3) 0·1N-HCl + 0·9N-NaCl (182).
(*c*) Di-*N*-methylaniline. (1) 1N-HCl (191 at 39,400 cm.$^{-1}$; $f = 0{\cdot}0028$); (2) 0·1N-HCl (192); (3) 0·1N-HCl + 0·9N-NaCl (188); (4) 0·1N-HCl + 0·9N-LiCl (197).
(*d*) Tri-*N*-methylanilinium chloride. (1) 10N-HCl (218 at 40,500 cm.$^{-1}$); (2) water (214; $f = 0{\cdot}0031$); (3) 4N-NaCl (207).
(*e*) 1-Naphthylamine. (1) 1N-HCl (502 at 33,200 cm.$^{-1}$); (2) 0·1N-HCl (465); (3) 0·1N-HCl + 0·9N-NaCl (490); (4) 0·1N-$HClO_4$ (480).
(*f*) 2-Naphthylamine. (1) 1N-HCl (405 at 33,600 cm.$^{-1}$); (2) 0·1N-HCl (402).

as its ability to solvate the charged positions of the ring in a more specific manner, when setting up a model for a calculation. The activation by NH_3^+ of the *meta*-position towards electrophilic attack must then be seen as a co-operative effect, specifically involving the attacking ion, and thus as a property of the activated complex.

[12] Biquard, *Bull. Soc. chim. France*, 1936, **3**, 909.
[13] Lanning and Cohen, *J. Biol. Chem.*, 1951, **189**, 111.
[14] Maschka, Stein, and Trauer, *Monatsh.*, 1954, **85**, 188.
[15] Anderson and Steedly, *J. Amer. Chem. Soc.*, 1949, **71**, 852.

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Experimental

Spectra were measured with a Uvispek spectrophotometer, and some of them checked with a Cary Model 11 instrument. Cell lengths were 2 cm. and concentrations about 0·002M. Some measurements with 5 cm. cells and correspondingly diluted solutions revealed no deviations from Beer's law.

Materials.—The substances are prone to oxidation and because the absorption bands studied are very weak, impurity concentrations of 0·01% or lower could detectably affect the spectra. The criteria of purity are thus much more stringent than those required for measurements of the same accuracy upon the free bases. The purification procedures were therefore repeated till the intensities agreed to within 1%.

Aniline, *N*-methylaniline, and di-*N*-methylaniline were obtained from commercial products, each of which, after a preliminary distillation, was fractionated at 760 ± 1 mm. in a 5-foot spinning-band column. The boiling range was less than 0·1°. They were stored over potassium hydroxide, and immediately before use were repeatedly distilled over zinc powder at a pressure of nitrogen of 10^{-4} mm. till colourless. Solutions were made up by weight, and remained spectroscopically stable for several hours. Tri-*N*-methylanilinium chloride was made from the iodide by ion exchange on a chloride resin (Amberlite IRA/400) and recrystallized from ethyl acetate. Each repurification cycle included further passages through the resin. The salt is deliquescent; a concentrated stock solution was analysed by titration of the chloride. 1-Naphthylamine was refluxed with water to remove the 2-isomer and distilled in nitrogen at 5 mm. The base is unstable, but the hydrochloride, purified by recrystallization from a 1 : 1 mixture of ethanol and concentrated hydrochloric acid, can be preserved in an inert atmosphere. 2-Naphthylamine was prepared by hydrolysing the purified *N*-acetyl derivative; the hydrochloride was recrystallized from concentrated hydrochloric acid. Inorganic chemicals were of Analytical Reagent grade.

We thank Mr. I. Reece of the N.S.W. University of Technology for the Cary spectrophotometer measurements.

Department of Chemistry, University of Sydney. [*Received, November 12th*, 1958.]

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403. *Vibrational Spectra and Assignments of Chloropicrin and Bromopicrin; Some Corrections and Additions.*

By Mrs. J. Mason (Banus), J. Dunderdale, and A. H. Castelli.

The assignments of two of the fundamental frequencies of the chloropicrin molecule have been altered, since the expected band contour types were derived from calculated moments of inertia, two of which have been shown by recent measurements of the molecular dimensions to be in the wrong order. This has necessitated alterations in two corresponding bromopicrin assignments.

Improved spectra of chloropicrin are presented.

Recalculation of the moments of inertia of the chloropicrin molecule, by use of recent measurements [2] on the electron diffraction of chloropicrin vapour, as well as those [3] on the microwave spectrum of chloroform, shows that the least moment is I_z, about the axis parallel to the C–N bond, and the intermediate one is I_y, about an axis in the ONO plane. In our assignment [1] of the vibrational spectrum of chloropicrin, for comparison with that of fluoropicrin, this relationship was reversed, and certain revisions are therefore necessary. Improved spectra of chloropicrin (Fig. 1) are now available.

Table 1 shows the moments of inertia, the symmetry factors,[4] the contour type for the

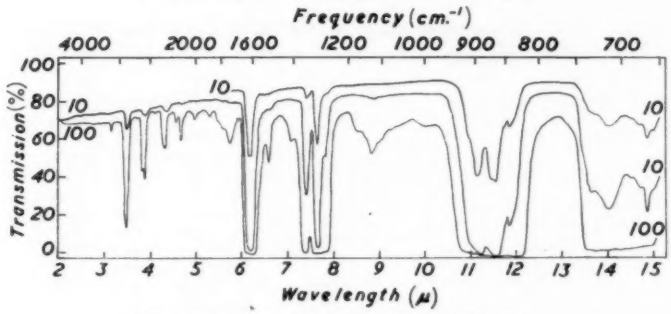
[1] Mason and Dunderdale, *J.*, 1956, 759.
[2] Barss, *J. Chem. Phys.*, 1957, **27**, 1260.
[3] Ghosh, Trambarulo, and Gordy, *J. Chem. Phys.*, 1952, **20**, 605.
[4] Badger and Zumwalt, *J. Chem. Phys.*, 1938, **6**, 711.

different symmetry species, and the separations of the P and R branch maxima for chloropicrin and also for bromopicrin, on the basis of the following " best values " for the dimensions (Å): CCl 1·76, CBr 1·92, CN (chloropicrin) 1·59, CN (bromopicrin) 1·62, NO 1·21; ∠ClCCl 110° 48′, ∠BrCBr 111°, ∠ONO 127°.

The order of the moments of inertia is unaltered for the new bromopicrin dimensions, so that the earlier band-envelope conclusions for that molecule can stand; the alterations in the PR separations are unimportant.

The most important consequence of the interchange of the A_1 and B_1 contour types in the chloropicrin spectrum is that the band at 677 cm.$^{-1}$ may now be assigned to the missing A_1 NO_2 deformation mode. This was previously ruled out because of the A type contour,

FIG. 1. *Infrared spectrum of chloropicrin gas.*



Numerals are absorbing paths (10 or 100 cm.).

and because it was thought unlikely that the frequency should be so high: the corresponding frequencies chosen for fluoropicrin and bromopicrin were 604 and 617 cm.$^{-1}$ respectively, and the correlation diagram for the $CX_3{\cdot}NO_2$ fundamentals [1] (X = H, D, F, Cl, Br) shows that the interaction between the two halves of the molecule is usually small. In addition,

TABLE 1. *Moments of inertia and band-envelope calculations.*

ρ	S	Axis	Moment of inertia (10^{-40} g. cm.^{2})	Contour type for vibns. parallel to axis	Symmetry species	PR separation at 70° (cm.$^{-1}$)
			Chloropicrin			
0·16	0·18	x	654 (648)	C	B_2	13·5
		y	591 (586)	B	B_1	14·6
		z	554 (551)	A	A_1	12·6
			Bromopicrin			
0·21	0·56	x	1161	B	B_2	10·8
		y	1097	A	B_1	9·1
		z	1391	C	A_1	10·0

The moments of inertia in parentheses are calculated from the electron diffraction figures for the chloropicrin dimensions; the calculated band envelopes are the same for these as for the " best values " given above.

the NO_2 symmetric deformation frequencies are 658 cm.$^{-1}$ for nitromethane [5] and 632 cm.$^{-1}$ for trideuteronitromethane,[5] and all the other vibrations (except the NO asymmetric stretching mode) have lower frequencies for the halogenopicrin molecules than for their lighter analogues, as one might expect. As a further argument against the assignment to the A_1 deformation mode, the 673 cm.$^{-1}$ Raman line [6] is depolarised, as for non-totally symmetric vibrations.

However, it is much more unlikely that the symmetric NO_2 deformation mode should

[5] Smith, Pan, and Nielsen, *J. Chem. Phys.*, 1950, **18**, 706.
[6] Wittek, *Z. physikal. Chem.*, 1942, **51**, *B*, 103.

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be inactive than that its frequency should be " high," and a high depolarisation factor of the 673 cm.$^{-1}$ Raman line (which was so weak that the polarisation factor was not measured) would not exclude the possibility that the vibration is totally symmetric.[7] We must therefore assume that this mode has a frequency of 677 cm.$^{-1}$ in the chloropicrin molecule, and examine the possibility that the frequencies chosen for fluoropicrin and bromopicrin (604 and 617 cm.$^{-1}$) are too low. In the fluoropicrin spectrum, however, there is no absorption between the 604 and the 750 cm.$^{-1}$ band system, and the assignment of the asymmetric NO_2 deformation mode to the latter is precluded by the much higher frequency, the demands of the CF symmetric deformation mode, and the good contour, which suggests that only one fundamental is involved.

In the bromopicrin spectrum there is a band at 669 cm.$^{-1}$, which was assigned to the

TABLE 2. *Frequency assignment of the vibrational spectrum of chloropicrin.*

IR, gas (cm.$^{-1}$)	IR, liq. (cm.$^{-1}$)	Raman,[a] liq. (cm.$^{-1}$)	DP[a]	Assignment		
3236 vw	—	—	—	$2 \times 1625 = 3250$		A_1
2916 s	—	—	—	$1625 + 1311 = 2936$		B_1
2703 vw	—	—	—	$1625 + 677 + 412 = 2714$	A_1	$[A_2]$
2646 m	—	—	—	$1625 + 1311 - 287 = 2649$	A_1	$[A_2]$
				$1625 + 717 + 296 = 2638$	A_1	$[A_2]$
2611 m	—	—	—	$2 \times 1311 = 2622$		A_1
2462 vw	—	—	—	$1625 + 846 = 2471$		B_1
2336 m	—	—	—	$1625 + 717 = 2342$	A_1	$[A_2]$
				$1625 + 2 \times 296 = 2217$		B_1
2208 w	—	—	—	$1625 + 296 + 287 = 2208$	A_1	$[A_2]$
				$1625 + 2 \times 287 = 2199$	B_1	B_2
2160 w	—	—	—	$1311 + 846 = 2157$		A_1
2119 w	—	—	—	$1625 + 296 + 202 = 2123$	A_1	$[A_2]$
2028 w	—	—	—	$1625 + 412 = 2037$	A_1	$[A_2]$
1905 w	—	—	—	$1625 + 287 = 1912$	A_1	$[A_2]$
1835 w 1802 w	—	—	—	$1625 + 202 = 1827$	A_1	$[A_2]$
1754 w	—	—	—	$1311 + 439 = 1750$		A_1
1701 vw	—	—	—	$2 \times 846 = 1694$		A_1
1632 1617 vs	1610 vs	1607 m	0·79	NO asym. str.		B_1
1520 m	—	—	—	$846 + 677 = 1523$		A_1
1500 w	—	—	—	$1311 + 202 = 1513$	B_1	B_2
1484 w	—	—	—	$846 + 439 + 202 = 1487$	B_1	B_2
1410 w	—	—	—	$1625 - 202 = 1423$	A_1	$[A_2]$
				$717 + 412 + 287 = 1416$	B_1	B_2
1387 w	—	—	—	$717 + 677 = 1394$	B_1	B_2
				$677 + 412 + 296 = 1385$	B_1	B_2
1361 1355 1349 m	1350 m	1345 m	—	$2 \times 677 = 1354$		A_1
1311 vs	1307 s	1310 s	0·49	NO sym. str.		A_1
1286 w	1277 w	1275 vw	—	$846 + 439 = 1285$		A_1
1243 1235 w	—	—	—	$846 + 412 = 1258$	B_1	B_2
1179 w	—	—	—	$1625 - 439 = 1186$		B_1
1155 w	—	—	—	$717 + 439 = 1156$	B_1	B_2
				$846 + 296 = 1142$		A_1
1133 w	—	—	—	$846 + 287 = 1133$	B_1	B_2
				$717 + 412 = 1129$	A_1	$[A_2]$
1116 w	—	1105 vw	—	$677 + 439 = 1116$		A_1
1070 vw	—	—	—	$677 + 2 \times 202 = 1081$		A_1
1057 w	—	—	—	$846 + 202 = 1048$	B_1	B_2
1038 vw	—	1025 vw	—	$846 + 202 = 1048$	B_1	B_2
				$1311 - 287 = 1024$	B_1	B_2
1007 vw	—	—	—	$1311 - 296 = 1015$		A_1
1003 w	—	—	—	$717 + 287 = 1004$	A_1	$[A_2]$
				$717 + 287 = 1004$	A_1	$[A_2]$

[7] Herzberg, " Infrared and Raman Spectra," Van Nostrand, New York, 1945, p. 270.

TABLE 2. (*Continued.*)

IR, gas (cm.$^{-1}$)	IR, liq. (cm.$^{-1}$)	Raman,[a] liq. (cm.$^{-1}$)	DP[a]		Assignment		
916							
909[c] } s	895 s	910 w	—	{	717 + 202 = 919	A_1	[A_2]
898				{	1311 − 412 = 899	B_1	B_2
888							
876 } vs							
868 }	858 s	865 vw	—	{	677 + 202 = 879	B_1	B_2
				{	2 × 439 = 878		A_1
				{	1311 − 439 = 872		A_1
—							
853 } m	842 m	843 s	0·27		CN str.		A_1
846 }							
840							
746·5							
741 } m	733 w	—	—		439 + 296 = 735		A_1
738 }							
—							
725 [c]s	—	—	—		439 + 287 = 726	B_1	B_2
717 s	707m	710s	0·70	—	CCl asym. str.	B_1	+ B_2
689 [c]m	—	—	—		412 + 287 = 699	A_1	[A_2]
682·5							
677 } m	670 m	673 w	dp		NO_2 sym. def.		A_1
670·5							
	523 w	516 w	—	{	296 + 202 = 498	B_1	B_2
				{	717 − 202 = 515	A_1	[A_2]
	445 m	439 vs	0·09		CCl sym. str.		A_1
		422 vw	—		NO_2 rocking	B_1	+ B_2
		296 s	0·66		CCl sym. def.		A_1
		287 s	dp		CCl_2 rocking	B_1	+ B_2
		202 vs	0·81		CCl asym. def.	B_1	+ B_2

[a] Wittek.[6] [c] New bands (see Experimental section). [ ] = Forbidden species.

CBr B_2 stretching mode (contour type B). The observed contour is, however, structureless, and might just as well be type A as type B, so that in view of the chloropicrin assignment this higher frequency must be considered preferable for the NO_2 symmetric deformation vibration in bromopicrin, particularly since the Raman line is polarised (DP = 0·75).

The descriptions of some of these vibrations, such as the NO_2 symmetric deformation and the CN stretching vibration, are only approximate, since it is likely that these two (for example) are coupled with each other and with lower A_1 frequencies in the chloro- and bromo-picrins; the CN stretching vibration for fluoropicrin, at 863 cm.$^{-1}$, is probably coupled with the CF symmetric deformation at 751 cm.$^{-1}$, which in turn may mix with the NO_2 symmetric deformation vibration at 604 cm.$^{-1}$.

Now that the 677 cm.$^{-1}$ frequency in the chloropicrin spectrum and the 669 cm.$^{-1}$ frequency in the bromopicrin spectrum are assigned to the NO_2 symmetric deformation modes, the other fundamentals previously assigned to these frequencies should probably be located elsewhere (the bands are of medium intensity only). These are the CCl B_1 and the CBr B_2 stretching modes. It is quite likely that for chloropicrin and for bromopicrin the B_1 and B_2 CX stretching modes are degenerate, or nearly so, for they are only split to the extent of 10 cm.$^{-1}$ in the fluoropicrin spectrum, and increase in weight of the atom X may well decrease the splitting. Thus both the CCl asymmetric stretching modes may be assigned to the very broad amorphous-looking band at 717 cm.$^{-1}$ in the chloropicrin spectrum, and both the CBr asymmetric stretching modes to the broad A- or C-type band at 617 cm.$^{-1}$ in the bromopicrin spectrum.

If the CN bond is significantly longer in chloropicrin and in bromopicrin than in fluoropicrin, the assignment of the CN stretching mode (863 cm.$^{-1}$ for fluoropicrin) should perhaps be transferred from 846 cm.$^{-1}$ (chloropicrin) and 840 cm.$^{-1}$ (bromopicrin) to lower frequencies. However, chloropicrin does not absorb in the region between the 846 and the 740 cm.$^{-1}$ band system, the 843 cm.$^{-1}$ Raman line is polarised, and this frequency cannot

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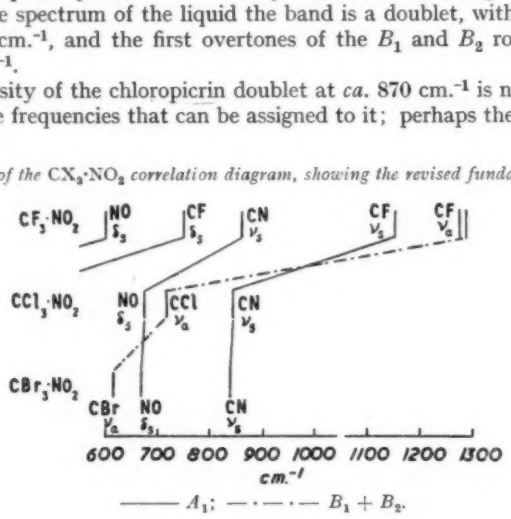
be assigned as a combination or difference tone, so the earlier assignment must stand. In the bromopicrin spectrum there is a band at 810 cm.$^{-1}$, the intensity of which is very high for a combination band, but there are several arguments against assigning this frequency to the CN stretching vibration, particularly in view of the chloropicrin value. One is that the greatest change in C–N bond length in the $CX_3{\cdot}NO_2$ series (change in mass seems less important in this connection) probably occurs between fluoropicrin and chloropicrin, so that one might expect the CN stretching frequencies to be closer for bromopicrin and chloropicrin than for chloropicrin and fluoropicrin. Another is that at least two combination tones and possibly two overtones may contribute to the high intensity of the 810 cm.$^{-1}$ band; in the spectrum of the liquid the band is a doublet, with peaks at 805—810 and at 790—795 cm.$^{-1}$, and the first overtones of the B_1 and B_2 rocking modes would absorb at 788 cm.$^{-1}$.

The high intensity of the chloropicrin doublet at *ca.* 870 cm.$^{-1}$ is not explained by the sum and difference frequencies that can be assigned to it; perhaps the results of a normal

FIG. 2. *Section of the* $CX_3{\cdot}NO_2$ *correlation diagram, showing the revised fundamental frequencies.*



co-ordinate treatment (which is in hand) of the $CX_3{\cdot}NO_2$ series will help to explain some of the oddities of the intensity distribution in the chloropicrin and bromopicrin spectra.

The frequency assignments for the vibrational bands of chloropicrin are shown in Table 2. Fig. 2 is a section of the halogenopicrin correlation diagram showing the revised chloropicrin and bromopicrin fundamentals, which agree with the non-crossing rule. A fuller account of the spectra, tables of fundamentals, and acknowledgment of previous work, is in the earlier paper.[1]

Experimental.—New measurements of the chloropicrin spectrum were made (by A. H. C.) with a Perkin-Elmer model 21 infrared spectrophotometer, with a sodium chloride prism. The chloropicrin (Eastman Kodak white label, re-distilled) was examined as a liquid in 0·254 mm. thickness, and as a vapour with an absorbing path of 10 or 100 cm. The new bands marked [c] in Table 2 were obtained with the 100 cm. absorbing path, in a multiple reflection cell.

One of us (A. H. C.) thanks the U.S. Army and Picatinny Arsenal for their co-operation. We thank also Delia M. Simpson (Mrs. J. N. Agar) for continued advice.

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DOVER, NEW JERSEY (A. H. C.). [*Received, November 26th,* 1958.]

404. *Aromatic Polyfluoro-compounds. Part II.* Pentafluorophenol.*

By E. J. Forbes, R. D. Richardson, M. Stacey, and J. C. Tatlow.

Hexafluorobenzene reacts with sodium methoxide to give pentafluoroanisole which when heated with aluminium chloride yields pentafluorophenol. This strongly acidic phenol has been fully characterised and shown to resist nucleophilic attack. Its hydrazinium salt is formed when pentafluoroanisole reacts with hydrazine hydrate.

The interesting fluorocarbon, hexafluorobenzene, has recently been prepared in quantity by Godsell, Stacey, and Tatlow [1] and by Hellmann *et al.*[2] Both groups of workers have shown that the molecule is reactive to nucleophilic agents.[1,3,4] An earlier report [5] had indicated that the molecule was stable to electrophilic attack, which is not surprising since substitution under such conditions would require the elimination of the fluorine cation (F^+). Nucleophilic attack, however, occurs readily when hexafluorobenzene reacts with sodium methoxide in methanol alone [1] or admixed with pyridine [3] or with potassium hydroxide in pyridine.[3] The first reaction, which gives a good yield of pentafluoroanisole, was used as the starting point for the present work. The last reaction gives a poor yield (20%) of pentafluorophenol. These reactions and others [4] which involve the elimination of a fluoride ion probably occur by way of a reactive intermediate complex analogous to that proposed by Bunnett and Zahler [6] for aromatic bimolecular nucleophilic substitution.

Pentafluorophenol was obtained as a liquid in 20% yield by Pummer and Wall [3] by demethylating pentafluoroanisole with hydriodic acid. Our own experiments using hydrobromic acid were no more successful. When, however, the anisole was heated with aluminium chloride without a solvent [7] pentafluorophenol was obtained in 60% yield as a solid, m. p. 39°, which was corrosive to the skin and very acidic. Its dissociation constant ($4{\cdot}79 \times 10^{-6}$ at 17·5) showed that it was considerably more acidic than phenol itself ($1{\cdot}3 \times 10^{-10}$ at 25° [8]) though slightly less acidic than pentachlorophenol ($5{\cdot}5 \times 10^{-6}$ at 25° [9]). This order of activity can be attributed to the greater power of electron-release through back-co-ordination in the fluorine than in the chlorine atom. Similar behaviour is shown by *p*-fluorobenzoic acid and *p*-fluorophenol, which are weaker acids than the corresponding chloro-compounds. Indeed, electron-release from fluorine by this mechanism is such as to make *p*-fluorophenol a weaker acid than phenol itself, and will be shown, in a subsequent communication, to have an important bearing on the orientation of disubstitution products obtained from pentafluorophenyl derivatives.

The low boiling point of pentafluorophenol, 145—146°, has been attributed to intramolecular hydrogen-bonding,[3] and the infrared spectrum, which shows bands at 3636 and 3448 cm.$^{-1}$ (free and bonded OH), indicates that this bonding is extensive. The ultraviolet spectra of pentafluorophenol and its phenoxide ion closely resemble those of phenol and its phenoxide ion. There is, however, an additional maximum at 350 mμ in the fluorophenol spectrum which is not shown by phenol itself but is shown by picric acid.

Pentafluorophenol was characterised by a number of derivatives, all of which were prepared by the usual methods. In addition, it formed a characteristic potassium salt

* Part I, *J.*, 1959, 166.

[1] Godsell, Tatlow, and Stacey, *Nature*, 1956, **178**, 199.
[2] Hellmann, Peters, Pummer, and Wall, *J. Amer. Chem. Soc.*, 1957, **79**, 5654.
[3] Pummer and Wall, *Science*, 1958, **127**, 643.
[4] Forbes, Richardson, and Tatlow, *Chem. and Ind.*, 1958, 630.
[5] Desirant, *Bull. Acad. roy. Belg., Classe Sci.*, 1955, **41**, 759.
[6] Bunnett and Zahler, *Chem. Rev.*, 1951, **49**, 273.
[7] Hartmann and Gattermann, *Ber.*, 1892, **25**, 3531.
[8] "Handbook of Chemistry and Physics," Chemical Rubber Publishing Co., Cleveland, Ohio, 39th edn., 1957.
[9] Tiessens, *Rev. Trav. chim.*, 1929, **48**, 1068.

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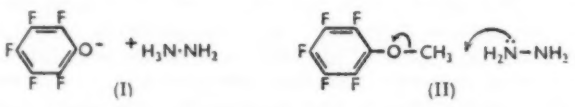
which crystallised from water as a dihydrate which could be dehydrated azeotropically with benzene. Other salts were formed with organic bases, even as weak as aniline.

The stability of pentafluorophenol towards attack by nucleophilic agents was marked. It was recovered unchanged after prolonged heating with strong alkali, presumably owing to the presence of the phenoxide ion which would render the nucleus resistant to nucleophilic attack. It seems likely that the dihydric phenol obtained by Pummer and Wall,[3] from the reaction between potassium hydroxide and hexafluorobenzene in pyridine–ethanol–water, arises from an attack of ethoxide ion on the intermediate pentafluorophenetole, followed by hydrolysis of the ether links with hydroxyl ion. The ready hydrolysis of the pentafluorophenyl ether link by nucleophilic agents is illustrated in the sequel.

It was thought that the powerful electron-withdrawing effect of the pentafluorophenyl nucleus might confer the properties of an ester or carboxylic acid on the anisole and phenol respectively: certainly, the acidity of the phenol is comparable to that of an aromatic carboxylic acid. When attempts were made to replace the hydroxyl group of the phenol with a chlorine atom no tractable product was isolated.

The reaction between pentafluoroanisole and hydrazine hydrate gave an interesting result. We had expected a straightforward displacement of the methoxyl group by hydrazine, as occurs in the reaction with 2 : 4-dinitroanisole.[10] However, the chief product of the reaction under a variety of conditions was the hydrazine salt (I) of pentafluorophenol. It was identified by converting it into the potassium salt of pentafluorophenol and isolating the hydrazine as its sulphate. The structure was confirmed when the compound was obtained directly from pentafluorophenol and hydrazine hydrate in the cold.



(I) (II)

This salt must be formed from the anisole by a direct displacement of phenoxide ion from the methyl group by the nucleophilic hydrazine molecule (cf. II). That the salt of hydrazine and not that of methylhydrazine is isolated must be due to the large excess of hydrazine which is usually employed in such reactions.

Experimental

Ultraviolet spectra were measured for ethanol solutions unless stated to the contrary.

Pentafluoroanisole.—A solution from sodium (7·1 g.) in absolute methanol (740 c.c.) was heated under reflux with hexafluorobenzene (49·8 g.). After 6 hr. the mixture was cooled and poured into a large volume of water. Pentafluoroanisole separated as an oil and was extracted with ether. The extract was dried and filtered, and the solvent removed. Distillation of the residue through a short column gave pure pentafluoroanisole (38·1 g., 72%), b. p. 138—139°, n_D^{20} 1·4090 (Found: C, 42·6; H, 1·7; F, 48·1. Calc. for $C_7H_3OF_5$: C, 42·4; H, 1·5; F, 48·0%). Godsell, Stacey, and Tatlow [1] give b. p. 155—157°, n_D^{18} 1·417, and Pummer and Wall [3] give b. p. 154—156°: these values were obtained on small samples and are too high. It had $\lambda_{max.}$ 266 mμ (ε 1023), $\nu_{max.}$ 3010 (aliphatic C–H stretching) and 1524 cm.$^{-1}$ (fluoro-aromatic ring breathing) (liquid film).

Pentafluorophenol.—(*a*) Pentafluoroanisole (8·75 g.) was heated with anhydrous aluminium chloride (8·5 g.) for 3 hr. at 120°, then cooled in iced water, and the pentafluorophenol was liberated by addition of iced water to the powdered mixture with stirring. The phenol was extracted with methylene chloride, the extract dried, and the solvent removed. Distillation of the residue gave pentafluorophenol (4·68 g., 58%), b. p. 142—144°, m. p. 38·5—39·5° (Found: F, 51·0%; equiv., 186. Calc. for C_6HOF_5: F, 51·6%; equiv., 184) [Pummer and Wall [3] give b. p. 72—73/48 mm. and 144—146° (micro-capillary)], $\lambda_{max.}$ 227, 269, and 350 mμ (ε 2640, 990, and 198, respectively): the phenoxide ion showed $\lambda_{max.}$ 228 mμ (ε 13,200) and 273 mμ (ε 2040)

[10] Borsche, *Ber.*, 1923, **56**, 1488.

(*c* 0·012 g./l. in 80% ethanolic 0·05N-sodium hydroxide). Infrared bands (liquid film) were at 3600 cm.$^{-1}$ (OH stretching) and 1515 cm.$^{-1}$ (fluoro-aromatic ring breathing).

(*b*) Pentafluoroanisole (2·2 g.) was heated under reflux with hydrobromic acid (20 c.c.; *d* 1·47) for 17 hr. After the heterogeneous mixture had been cooled, the aqueous layer was decanted from an oil. A solution of the oil in ether was extracted with 2N-sodium hydroxide (30 c.c.). From the ether layer was then obtained unchanged pentafluoroanisole (0·5 g.), and from the alkaline extract acidification gave pentafluorophenol (0·2 g.), identified as its toluene-*p*-sulphonate, m. p. and mixed m. p. 62—63°.

Potassium pentafluorophenoxide dihydrate was obtained when 6N-potassium hydroxide (5 c.c.) was added slowly to a solution of pentafluorophenol (0·5 g.) in 6N-potassium hydroxide (3 c.c.). The precipitated salt, crystallised from a little water, had m. p. 245° (decomp.) (Found: C, 27·9; H, 1·6; F, 36·7. $C_6OF_5K,2H_2O$ requires C, 27·9; H, 1·6; F, 36·8%). The *monohydrate*, m. p. 248° (decomp.), was obtained from the dihydrate at 110°/18 mm. in 3 hr. (Found: C, 30·2; H, 1·1; F, 39·5. C_6OF_5K,H_2O requires C, 30·0; H, 1·2; F, 39·6%). The anhydrous *salt* was obtained when the dihydrate was boiled with benzene for 5 hr.: removal of the liquid phase gave a white powder which, crystallised from acetone, had m. p. 242° (decomp.) (Found: F, 42·8. C_6OF_5K requires F, 42·8%).

The *toluene*-p-*sulphonate* of pentafluorophenol was obtained when the potassium salt dihydrate (0·31 g.), toluene-*p*-sulphonyl chloride (0·28 g.), and water (2 c.c.) were heated with stirring on a steam-bath for 5 hr. A solution of the product in light petroleum (b. p. 40—60°) was washed with concentrated ammonia and then evaporated to dryness. Recrystallisation of the residue from ethanol afforded an analytical specimen, m. p. 64—65° (Found: C, 46·1; H, 2·1; F, 27·8. $C_{13}H_7O_3SF_5$ requires C, 46·2; H, 2·1; F, 28·1%). The p-*nitrobenzyl ether*, prepared by heating the potassium salt of the phenol with *p*-nitrobenzyl bromide in aqueous ethanol for 1 hr., crystallised from ethanol in pale yellow plates, m. p. 57° (Found: C, 48·5; H, 1·8. $C_{13}H_6O_3NF_5$ requires C, 48·9; H, 1·9%). The benzoate (Schotten–Baumann procedure) had m. p. 70·5—71·5° after three recrystallisations from aqueous ethanol (Found: C, 54·4; H, 1·7. Calc. for $C_{13}H_5O_2F_5$: C, 54·2; H, 1·7%) (Pummer and Wall [3] cite m. p. 76·5—78·2°). The *anilinium salt* crystallised from a little water in needles, m. p. 74° (Found: C, 51·9; H, 2·9. $C_{12}H_8ONF_5$ requires C, 52·0; H, 2·9%).

Hydrazinium Pentafluorophenoxide.—Pentafluoroanisole (5·0 g.), 80% w/w hydrazine hydrate (18·0 g.), and sufficient ethyl alcohol (*ca.* 5 ml.) to render the mixture homogeneous were heated together under reflux for 5 hr., then cooled, poured into an equal volume of water, and extracted with methylene chloride (6 × 10 ml.). The aqueous layer was continuously extracted with methylene chloride for 80 hr. From this extraction a colourless solid was obtained, which crystallised in the methylene chloride. Purification by crystallisation, or by sublimation at 80°/0·2 mm., gave *hydrazinium pentafluorophenoxide* (3·32 g., 61%), m. p. 157—158° (subl.) (Found: C, 33·3; H, 2·4. $C_6H_5ON_2F_5$ requires C, 33·4; H, 2·3%), $\lambda_{max.}$ 230 and 269 mμ (ε 7700 and 1390, respectively).

With less hydrazine hydrate and at a lower concentration the yield of hydrazine pentafluorophenoxide dropped to 31%.

Concentrated sulphuric acid was added dropwise to a solution of hydrazine pentafluorophenoxide (0·1 g.) in ethanol (2 c.c.) until no more solid was formed. The colourless precipitate was recrystallised from hot water to give large colourless crystals of hydrazine sulphate (0·03 g.), m. p. and mixed m. p. 255°. The infrared spectra of these compounds were identical.

Hydrazinium pentafluorophenoxide (0·3 g.) was warmed gently with 6N-potassium hydroxide (4 c.c.) for a few minutes. On cooling, a colourless precipitate was formed which recrystallised from a little water. Potassium pentafluorophenoxide dihydrate was thereby obtained, having m. p. and mixed m. p. 245° (decomp.).

A solution of 100% hydrazine hydrate (0·089 g.), and pentafluorophenol (0·12 g.) was continuously extracted with methylene chloride for 48 hr. The solid which was precipitated in the boiling flask was collected and sublimed at 80°/0·05 mm., to afford hydrazinium pentafluorophenoxide (0·09 g., 64%), m. p. and mixed m. p. with the product isolated from the reaction between hydrazine hydrate and pentafluoroanisole, 157—158°. The infrared spectra of the two solids were identical.

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CHEMISTRY DEPARTMENT, THE UNIVERSITY, BIRMINGHAM, 15. [*Received, November 27th,* 1958.]

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405. 5 : 6 : 7 : 8-*Tetrahydro*-8-*methylindane*-1 : 5-*dione*.

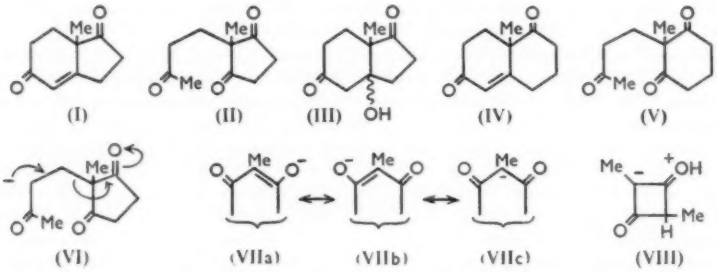
By C. B. C. Boyce and J. S. Whitehurst.

5 : 6 : 7 : 8-Tetrahydro-8-methylindane-1 : 5-dione has been synthesised in good yield. The naphthalene analogue could not be prepared by using the same conditions, and differences between the two ring systems are discussed.

Acklin, Prelog, and Prieto [1] have recently prepared the indane (I); we had also obtained this substance, by a less tedious method.

2-Methyl*cyclo*pentane-1 : 3-dione was prepared from 2-methyl*cyclo*pentane-1 : 3 : 4-trione [2] (*a*) by vigorous acid-catalysed hydrogenolysis and (*b*) by Wolff–Kishner [3] reduction of its semicarbazone. For the latter, the slow addition of semicarbazide to the trione proved vital to the success of the subsequent decomposition. The alkali-catalysed addition of methyl vinyl ketone to the dione was almost quantitative in hot methanol yielding the crystalline trione [4] (II) and this was smoothly cyclised by toluene-*p*-sulphonic acid in refluxing benzene. The overall yield from the dione was about 70% and the entire operation could be completed within a day.

Heating the trione (II) with oxalic acid [5] or boric acid gave only a small yield of the indane (I). When passed through alumina the trione (II) gave some ketol [5] (III) but the separation of the two was difficult. The ketol (III), which from its constitution might have been expected to undergo ready dehydration with thionyl chloride–pyridine,[6] in practice yielded some required product (I) and much 2-methyl*cyclo*pentane-1 : 3-dione. Clearly the formation of the latter involves a reverse Michael reaction. However, with toluene-*p*-sulphonic acid in hot benzene the ketol (III) readily gave the indane (I).



Similar experiments designed to provide the octalin (IV) gave different results. This compound is readily made from 2-methyl*cyclo*hexane-1 : 3-dione and 4-diethylamino-butan-2-one.[7,8] Under similar conditions 2-methyl*cyclo*pentane-1 : 3-dione gave a dark product from which the indane (I) could only be obtained in low yield. Moreover, the trione (V), prepared from methyl vinyl ketone and 2-methyl*cyclo*hexane-1 : 3-dione,[9] did not lose water when treated with toluene-*p*-sulphonic acid in benzene. Further, whereas diethylamine–pyridine is known to cyclise the trione (V) to the octalin (IV),[7] a similar experiment with the trione (II) gave principally the product, 2-methyl*cyclo*pentane-1 : 3-dione, of retro-Michael reaction.

[1] Acklin, Prelog, and Prieto, *Helv. Chim. Acta*, 1958, **41**, 1416.
[2] Butz and Orchin, *J. Amer. Chem. Soc.*, 1943, **65**, 2296.
[3] Panouse and Sannié, *Bull. Soc. chim. France*, 1955, 1036.
[4] Cf. ref. 1.
[5] Wieland and Miescher, *Helv. Chim. Acta*, 1950, **33**, 2215.
[6] Darzens, *Compt. rend.*, 1911, **152**, 1601.
[7] Swaminanthan and Newman, *Tetrahedron*, 1958, **2**, 65; U.S.P. 2,714,615/1955.
[8] Unpublished work of Robinson, quoted by Cocker and Halsall, *J.*, 1957, 3441.
[9] Nazarov, Zav'yalov, Burmistrova, Gurvich, and Shmonina, *Zhur. obshchei Khim.*, 1956, **26**, 1441.

The explanation for these reverse Michael reactions (*i.e.*, VI) is probably to be found in the stability of the anion from 2-methyl*cyclo*pentane-1 : 3-dione. Fully developed mesomerism in the system (VIIa—VIIb) requires the structures to be planar. Both ring systems satisfy this requirement but in addition (leaving aside the nature of carbanions themselves [10]) the *cyclo*pentane system is also planar in the mesomeric anion (VIIc), and this will make a greater contribution to the ground state than in the corresponding *cyclo*hexane case. The published values of the dissociation constants of *cyclo*hexane-1 : 3-dione [11] (5·26) and *cyclo*pentane-1 : 3-dione [12] (4·5) support this contention. Tetronic acid [13] (pK 3·76) possesses a similar cyclic system and 2 : 4-dimethyl*cyclo*butane-1 : 3-dione [14] is a surprisingly strong acid (pK 2·8) and behaves as a typical monoenol. To account for its acidity (VIII) has been invoked as an effective contributor to the ground state. The anion of (VIII) is clearly analogous to (VIIc).

Experimental

Ethyl 4-methyl-2 : 3 : 5-trioxo*cyclo*pentylglyoxylate [2] was hydrolysed by 2N-aqueous hydrochloric acid to the trione, m. p. 77—79° (overall yield from butan-2-one, 26%).

2-*Methyl*cyclo*pentane*-1 : 3-*dione*.—(*a*) A solution of semicarbazide hydrochloride (112 g.) and sodium acetate (150 g.) was added at 20° during 30 min. to well-stirred 2-methyl*cyclo*pentane-1 : 3 : 4-trione monohydrate (144 g.) in ethanol (1000 ml.) and water (500 ml.). After stirring for a further hour the pale yellow semicarbazone was collected, washed with aqueous ethanol, and dried in a vacuum oven (yield 178 g., 97%). The semicarbazone (80 g.) was added to potassium hydroxide (80 g.), dissolved in ethylene glycol (800 ml.), at 130°. The solution was heated at 150° for 30 min. and at 180° for 1 hr., and then all solvent was removed (0·05 mm.). The residue in water (400 ml.) was acidified to pH 3 with hydrochloric acid, and the precipitate crystallised from water; the dione had m. p. 208—209°. The average yield from 20 such runs involving variations of the above procedure was 51% (Panouse and Sannié [3] claim 86%).

(*b*) The trione monohydrate (1·44 g.) was hydrogenated (20°; 760 mm.) with reduced Adams's catalyst (100 mg.) in acetic acid (25 ml.) containing perchloric acid (0·5 ml.). Absorption, rapid at first, ceased after 6 hr. Treatment with 50% potassium hydroxide (to remove perchloric acid) and subsequent concentration gave a pale brown oil which crystallised from water (0·35 g., 31%; m. p. 205—207°).

5 : 6 : 7 : 8-*Tetrahydro*-8-*methylindane*-1 : 5-*dione*.—(*a*) The dione (40 g.), 4-diethylaminobutan-2-one (62·4 g.), pyridine (30 ml.), and benzene (500 ml.) were refluxed for 18 hr. After being cooled and washed with 2N-hydrochloric acid the organic layer was dried ($MgSO_4$) and distilled. The liquid product was crystallised from ether–light petroleum (b. p. 40—60°) (2 : 1), yielding the pure compound (10·3 g., 17%), m. p. 73°. The mother liquors darkened rapidly in air and extensive chromatography on alumina did not furnish any more material. (A nitrogen atmosphere had no appreciable effect on the yield or quality of the product.)

(*b*) A mixture of 2-methyl*cyclo*pentane-1 : 3-dione (65 g.), anhydrous methanol (250 ml.), freshly distilled methyl vinyl ketone (61·5 g.), and potassium hydroxide (3 pellets) was refluxed for 5 hr. The solvent was removed *in vacuo*, and the solid residue treated with water and chloroform. The organic layer, after being dried ($MgSO_4$), was distilled. 2-Methyl-2-3′-oxobutyl*cyclo*pentane-1 : 3-dione was collected at 108—112°/0·1 mm. and solidified on cooling (88 g., 83%). An analytical specimen had m. p. 117—118° (ethyl acetate) (Found: C, 65·9; H, 8·1. Calc. for $C_{10}H_{14}O_3$: C, 65·9; H, 7·7%). Infrared absorption ($cm.^{-1}$): 1762 (*cyclo*pentanone); 1732 (carbonyl); no hydroxyl absorption.

The compound (45 g.) in benzene (250 ml.) was refluxed with toluene-*p*-sulphonic acid (2 g.), a modified Dean–Stark water separator being used. After 2 hr. more toluene-*p*-sulphonic acid (2 g.) was added, the theoretical amount of water being collected after 5 hr. The solvent was

[10] Leffler, "The Reactive Intermediates of Organic Chemistry," Interscience Publishers, New York, 1956; Ziegler and Wenz, *Chem. Ber.*, 1950, **83**, 354.
[11] Schwarzenbach and Lutz, *Helv. Chim. Acta*, 1940, **23**, 1147.
[12] Waller, Wolf, Hutchings, Williams, Broschard, and Goldman, *J. Amer. Chem. Soc.*, 1952, **74**, 4978.
[13] Kumler, *J. Amer. Chem. Soc.*, 1935, **57**, 1929; 1938, **60**, 859; Schwarzenbach and Lutz, *Helv. Chim. Acta*, 1940, **23**, 1162.
[14] Woodward and Small, *J. Amer. Chem. Soc.*, 1950, **72**, 1297.

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removed *in vacuo*, and crystallisation of the oily residue from 2 : 1 ether–light petroleum deposited large crystals of 5 : 6 : 7 : 8-tetrahydro-8-methylindane-1 : 5-dione (33·5 g., 83%), m. p. 72—73°.

2-Methyl-2-3′-oxobutyl*cyclo*hexane-1 : 3-dione was made similarly in 85% yield. It was an oil, b. p. 114—118°/0·01 mm., n_D^{16} 1·5110, and had the expected infrared absorption. Newman [7] gives b. p. 114—116°/0·1 mm.

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THE WASHINGTON SINGER LABORATORIES, EXETER. [*Received, December 5th*, 1958.]

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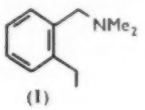
406. *The Hofmann Degradation of* 1 : 2 : 3 : 4-*Tetrahydro*-1 : 2-*dimethyl*isoquinoline.

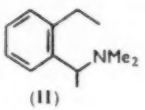
By G. CHILDS and E. J. FORBES.

Syntheses of 1- and 2-*o*-ethylphenylethyldimethylamine are described. The former amine is shown to be the dihydromethine of the Hofmann degradation product of 1 : 2 : 3 : 4-tetrahydro-1 : 2-dimethyl*iso*quinoline; the latter is shown to be the product of reduction of this *iso*quinoline with sodium and liquid ammonia.

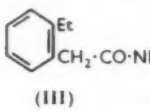
ELSNER, STRAUSS, and FORBES [1] prepared a number of pure *o*-dialkylated benzenes by various routes. One route to *o*-diethylbenzene used *iso*quinoline as the starting material, the intermediate 1 : 2 : 3 : 4-tetrahydro-1 : 2-dimethyl*iso*quinoline being subjected to Hofmann degradation and the resulting styrene reduced. The resulting further intermediate would eventually give *o*-diethylbenzene whether it had structure (I) or (II). It has now been shown, by unequivocal syntheses of the amines (I) and (II), that the dihydromethine is in fact 1-*o*-ethylphenylethyldimethylamine (II).



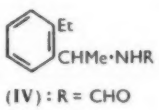
(I)



(II)



(III)



(IV) : R = CHO
(V) : R = H

2-Ethylphenethyldimethylamine (I) was synthesised as follows. *o*-Ethylaniline was converted by the Sandmeyer reaction into the nitrile, which was hydrolysed to *o*-ethylbenzoic acid. Hydrolysis of *ortho*-substituted benzonitriles is known to be difficult [2] and require drastic conditions. *o*-Ethylbenzonitrile was little affected by strong acids, and alkali (under the usual conditions) gave only the amide. The amide proved resistant to acid-hydrolysis, and even nitrous acid, but prolonged heating with concentrated alkali afforded good yields of the acid. These results confirm previous work [3] that for sterically hindered nitriles hydrolysis to the amide is easier than hydrolysis of the amide to the acid.

o-Ethylbenzoic acid was converted into *o*-ethylphenylacetamide (III) by the Arndt–Eistert procedure, without isolation of the intermediate diazoketone. Reduction of the amide (III) to 2-ethylphenethylamine with lithium aluminium hydride proceeded smoothly, as also did methylation of the primary amine with formaldehyde and formic acid [4] (when

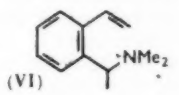
[1] Elsner, Strauss, and Forbes, *J.*, 1957, 578.
[2] Pfeiffer, Engelhardt, and Alfuss, *Annalen*, 1928, **467**, 158.
[3] Sperber, Papa, and Schwenk, *J. Amer. Chem. Soc.*, 1948, **70**, 3091.
[4] Clarke, Gillespie, and Weisshaus, *ibid.*, 1933, **55**, 4571.

applied to phenethylamines this methylation procedure often yields the tetrahydro-1-methyl*iso*quinoline;[5] none of this was obtained from the present reaction). The methiodide of the amine (I) was not identical with that obtained by Elsner *et al.*[1]

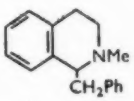
Analyses on rigorously dried specimens indicated that the methiodide of the amine (I) retained most tenaciously half a molecule of water of crystallisation whose presence was clear in the infrared spectrum (band at 3560 cm.$^{-1}$). The same hydrate was obtained when 1 : 2 : 3 : 4-tetrahydro-1 : 2-dimethyl*iso*quinoline methiodide was treated with sodium and liquid ammonia and the product converted into its methiodide. This reaction has been shown[6] to give the same product as Emde reduction[7] (with sodium amalgam or catalytically) and results in the cleavage of the 1 : 2-carbon–nitrogen bond. Thus the amine (I) is the expected product in the present case.

For the preparation of the amine (II), *o*-ethylbenzonitrile was converted into *o*-ethylacetophenone, by an improvement of the known method[8] using methyl-lithium in place of the Grignard reagent. The intermediate ketimine was fairly stable to hydrolysis, a fact which has been previously noted for compounds obtained from sterically hindered nitriles:[9] boiling with dilute acid was necessary for complete hydrolysis.

2-Ethylacetophenone was converted into 1-*o*-ethylphenylethylamine (V; R = H) by the Leuckart procedure.[10] The intermediate *N*-formyl derivative (IV; R = CHO) was not isolated but was hydrolysed to the free base, which was methylated to give 1-*o*-ethylphenylethyldimethylamine (II). The methiodide of the base (II) was identical with that prepared by Elsner, Strauss, and Forbes.[1]



(VI)



(VII)

Thus the styrene (VI) is the product of Hofmann degradation of 1 : 2 : 3 : 4-tetrahydro-1 : 2-dimethyl*iso*quinoline. This result could not have been predicted by the Hofmann rule (formation of the least substituted olefin) since both possible products would be monosubstituted. In general, however, the reaction proceeds in the direction which utilises the most acidic hydrogen β to the quaternary centre, unless the attacking base is so large that steric considerations become important.[11] On this basis the production of the styrene (VI) is understandable since it involves an acidic benzyl-hydrogen atom. That α-phenyl groups may also influence the course of Hofmann pyrolysis[12] is well illustrated in the benzyl*iso*quinoline series (*e.g.*, VII), where the stilbene is formed almost to the exclusion of the styrene.[13]

Experimental

o-Ethylbenzoic Acid.—A solution of *o*-ethylbenzonitrile[14] (5 g.) in ethanol (10 c.c.) was heated with potassium hydroxide (5 g.) in water (5 c.c.) and ethanol (30 c.c.) for 24 hr. Potassium hydroxide (5 g.) was then added and heating continued for a further 24 hr. (ammonia was then no longer being evolved). Removal of the alcohol, followed by the addition of dilute hydrochloric acid to the residue, gave *o*-ethylbenzoic acid (4·08 g.), which afforded plates, m. p. 63—64°, from light petroleum.

[5] Forbes, *J.*, 1955, **3926**; Osgerby and Pauson, *Chem. and Ind.*, 1958, 1144.
[6] Clayson, *J.*, 1949, 2016.
[7] Emde, *Annalen*, 1912, **391**, 88; Emde and Kull, *Arch. Pharm.*, 1936, **274**, 173.
[8] Birch, Dean, Fidler, and Lowry, *J. Amer. Chem. Soc.*, 1949, **71**, 1362.
[9] Ramart-Lucas and Salmon-Legagneur, *Compt. rend.*, 1927, **184**, 102.
[10] Ingersoll, Brown, Kim, Beauchamp, and Jennings, *J. Amer. Chem. Soc.*, 1936, **58**, 1808.
[11] Brown, *J.*, 1956, 1248.
[12] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, p. 447.
[13] Decker and Galatty, *Ber.*, 1909, **42**, 1179.
[14] Clarke and Read, *Org. Synth.*, Coll. Vol. I, 2nd edn., p. 514.

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Heating the mixture for only 16 hr. gave *o*-ethylbenzamide, m. p. 147—148° (lit.,[15] 153°), in almost quantitative yield.

o-*Ethylphenylacetamide*.—*o*-Ethylbenzoic acid (17 g.) was heated under reflux with thionyl chloride (15 c.c.) for 3 hr. Distillation then gave *o*-ethylbenzoyl chloride (16 g.), b. p. 118°/15 mm. A solution of this in dry ether (20 c.c.) was added dropwise to a solution of diazomethane (from 60 g. of methylnitrosourea) in ether (500 c.c.) at 0°. After being kept overnight, the solution was evaporated, and the residual diazoketone was dissolved in dioxan (100 c.c.). To this solution was added ammonia (150 c.c.; *d* 0·880) and 10% aqueous silver nitrate (30 c.c.). The mixture was kept at 80° for 2 hr., then boiled for 1 hr. Working up in the usual manner gave o-*ethylphenylacetamide* (12 g.), needles, (from water), m. p. 136° (Found: C, 73·5; H, 8·0; N, 8·4. $C_{10}H_{13}ON$ requires C, 73·2; H, 7·9; N, 8·5%).

2-*Ethylphenethylamine*. A solution of *o*-ethylphenylacetamide (7·5 g.) in anhydrous tetrahydrofuran (100 c.c.) was added slowly with stirring to a suspension of lithium aluminium hydride (2·2 g.) in tetrahydrofuran (30 c.c.). The mixture was then heated under reflux for 4—5 hr. After replacement of the tetrahydrofuran by ether, the mixture was decomposed with water and treated with alkali. The aqueous layer was extracted overnight with ether. The combined ethereal layers yielded 2-ethylphenethylamine (4·6 g.), b. p. 142—143°/1 mm. The *picrate* crystallised from water in needles, m. p. 171° (Found: C, 50·5; H, 4·7; N, 14·5. $C_{16}H_{18}O_7N_4$ requires C, 50·8; H, 4·8; N, 14·8%).

2-*Ethylphenethyldimethylamine* (I).—2-Ethylphenethylamine (2·5 g.) in 90% formic acid (5·6 g.) and 40% aqueous formaldehyde (1·8 g.) was heated on a steam-bath overnight. Concentrated hydrochloric acid was added to the cooled mixture, which was next evaporated under reduced pressure. A solution of the residue in water was rendered alkaline and extracted with ether (3 × 20 c.c.). The combined extracts were dried and filtered. To a portion of the filtrate was added methyl iodide, affording 2-*ethylphenethyltrimethylammonium iodide*, plates (from ethyl acetate–ethanol), m. p. 194—195° (Found: C, 47·7; H, 6·7; N, 4·3; I, 38·4. $C_{13}H_{22}NI,\frac{1}{2}H_2O$ requires C, 47·6; H, 7·0; N, 4·3; I, 38·7%), ν 3560 cm.$^{-1}$.

The *picrate*, obtained from an ethereal solution of the base, crystallised from water in needles, m. p. 118—118·5° (Found: C, 53·0; H, 5·5; N, 14·0. $C_{18}H_{22}O_7N_4$ requires C, 53·2; H, 5·4; N, 13·8%).

Reduction of 1 : 2 : 3 : 4-*Tetrahydro*-1 : 2 : 2-*trimethylisoquinoline Iodide with Sodium in Liquid Ammonia*.—To a solution of the methiodide (4 g.) in liquid ammonia (100 c.c.) at −70° was added sodium in small pieces until the blue colour remained permanently. After 1 hr., a crystal of ferric nitrate and then solid ammonium chloride were added to the solution. When the ammonia had evaporated, the residue was extracted with ether (2 × 50 c.c.). The extracts were dried and distilled to give 2-ethylphenethyldimethylamine, b. p. 128—129°/12 mm. Its methiodide gave m. p. 195—195·5°, undepressed on admixture with the specimen obtained as above (Found: C, 47·7; H, 7·0%). The picrate had m. p. and mixed m. p. 119°.

2-*Ethylacetophenone*.—A solution of methyl-lithium [from lithium (3·0 g.)] in ether (40 c.c.) was added dropwise under nitrogen to a solution of *o*-ethylbenzonitrile (14 g.) in ether (30 c.c.) with stirring. After 0·5 hr., the mixture was treated with water, followed by 4N-hydrochloric acid (20 c.c.). The ether layer was removed and the aqueous layer extracted with ether. The combined ethereal extracts were dried, filtered, and evaporated to an oil, which was heated under reflux with dilute hydrochloric acid (30 c.c.) for 45 min. Working up in the usual manner gave 2-ethylacetophenone (10·2 g., 65%), b. p. 120—122°/13 mm. The semicarbazone crystallised from methanol in needles, m. p. 180—181° (Found: N, 21·0. Calc. for $C_{11}H_{15}ON_3$: N, 20·5%); Baddeley [16] cites m. p. 182°. The 2 : 4-*dinitrophenylhydrazone* crystallised from aqueous methanol in orange needles, m. p. 118—119° (Found: C, 58·7; H, 5·3; N, 17·0. $C_{16}H_{16}O_4N_4$ requires C, 58·5; H, 4·9; N, 17·1%).

1-o-*Ethylphenylethylamine*.—2-Ethylacetophenone (5·9 g.) was heated for 10 hr. at *ca.* 180° with ammonium formate prepared from ammonium carbonate (8·6 g.) and 90% formic acid (9 g.). The cooled mixture was triturated with water (50 c.c.), and the aqueous layer discarded. The organic layer was heated under reflux with concentrated hydrochloric acid (40 c.c.) for 1·5 hr. On cooling, the solution was extracted with benzene, then basified. The precipitated oil was extracted with ether. Treating the dried ethereal extract with dry hydrogen chloride gave 1-o-*ethylphenylethylamine hydrochloride* (3·8 g.), which crystallised from ethyl

[15] Willard and Maresh, *J. Amer. Chem. Soc.*, 1940, **62**, 1253.
[16] Baddeley, *J.*, 1944, 232.

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acetate–ethanol in needles, m. p. 175° (Found: C, 64·2; H, 8·6; N, 7·7. $C_{10}H_{14}NCl$ requires C, 64·7; H, 8·6; N, 7·6%). The *picrate* crystallised from water in needles, m. p. 195—196° (Found: C, 50·8; H, 4·8; N, 14·8. $C_{16}H_{18}O_7N_4$ requires C, 50·8; H, 4·6; N, 14·8%).

1-o-*Ethylphenylethyldimethylamine* (II).—1-*o*-Ethylphenylethylamine (2·5 g.), 40% aqueous formaldehyde (1·8 g.), and 90% formic acid (5·6 g.) were heated on a steam-bath overnight. On cooling, the mixture was acidified and extracted with ether. Basification of the aqueous layer gave an oil, which was taken up in ether. When methyl iodide was added to the dried ethereal extract 1-o-*ethylphenylethyltrimethylammonium iodide* was obtained as a solid, which crystallised from ethyl acetate–ethanol in plates, m. p. 173°, undepressed on admixture with "*x*-(*o*-ethylphenyl)ethyltrimethylammonium iodide" prepared by Elsner *et al.*[1] (Found: N, 4·1; I, 39·8. $C_{13}H_{22}NI$ required N, 4·4; I, 39·8%).

The *hydrochloride* crystallised from ethyl acetate–ethanol in needles, m. p. 196° (Found: C, 67·5; H, 9·3; N, 6·7. $C_{12}H_{20}NCl$ requires C, 67·5; H, 9·4; N, 6·6%). The *picrate* crystallised from water in needles, m. p. 183° (Found: C, 53·4; H, 5·4; N, 14·1. $C_{18}H_{22}O_7N_4$ requires C, 53·2; H, 5·4; N, 13·8%).

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407. *The Behaviour of Ammonia in Gas Chromatography. Part I. Ammine Formation in Columns containing Solutions of Silver Nitrate in Benzyl Cyanide.*

By L. A. DU PLESSIS and A. H. SPONG.

When ammonia is passed into a freshly packed column containing silver nitrate in benzyl cyanide, it is permanently absorbed. After this absorption, the column retards further samples to produce a chromatogram consisting of a peak followed by a lower plateau. Decrease in sample size causes the peak to shrink until, at a critical sample size, it vanishes, leaving only the plateau. These results are interpreted as indicating the formation of a lower, stable ammine and a higher, unstable one related by the reaction $AgZ(NH_3)_x + 0{\cdot}5NH_3 \rightleftharpoons AgZ(NH_3)_{x+0{\cdot}5}$, the dissociation pressure of the higher ammine being approximately $5{\cdot}7 \times 10^{-3}$ atm.

SOLUTIONS of silver salts have been used as fixed phases in gas–liquid chromatography for the separation of olefins and other organic compounds.[1] Since such salts form ammines, their solutions suggest themselves for the chromatography of gaseous mixtures containing ammonia, and their use in this way has yielded unusual chromatograms which can be interpreted in terms of ammine formation. The results reported here were obtained at room temperature with solutions of silver nitrate in benzyl cyanide, and indicate the formation of at least two ammines, as is common with silver salts.[2]

Packings were generally prepared from 150·0 g. of fine glass beads as support, 5·00 ml. of benzyl cyanide, and a weighed amount (20—60 mg.) of silver nitrate, and packed by vibration in three weighed sections 90·0, 81·0, and 83·0 cm. long. Since the packings were not free-flowing, it was not possible to obtain uniform columns (linear density varied from 0·512 to 0·542 g. cm.$^{-1}$, permeability[3] by up to 22% from mean value). Coarser beads could be more

[1] Bradford, Harvey, and Chalkley, *J. Inst. Petroleum*, 1955, **41**, 80; van de Craats, *Analyt. Chim. Acta*, 1956, **14**, 136; Gil-Av, Herling, and Shabtai, *Chem. and Ind.*, 1957, 1483; Tenney, *Analyt. Chem.*, 1958, **30**, 2; Bednas and Russell, *Canad. J. Chem.*, 1958, **36**, 1272; Phillips in "Gas Chromatography" (Coates, Noebels, and Fagerson, eds.), Academic Press Inc., New York, 1958, p. 51.

[2] "International Critical Tables," McGraw-Hill Book Company Inc., New York, 1930, Vol. VII, pp. 267—269.

[3] Keulemans, "Gas Chromatography," Reinhold Publishing Corporation, New York, 1957, Chapter 5.

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uniformly packed, but gave poor results because of their small specific area. Crushed fire-brick adsorbed ammonia too strongly for use as a support; impregnation with alkali reduced adsorption, but was not used because of possible reaction of the alkali with the silver salt.

Nitrogen was used as carrier gas and its flow-rate corrected to ml. min.$^{-1}$ of dry gas at column temperature and atmospheric pressure.

Results

A new packing absorbs a small amount of ammonia permanently, as is shown by non-emergence of a small sample. The amount absorbed cannot be measured, because the absorption

Fig. 1.

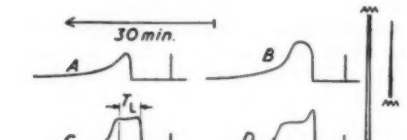

Fig. 2.

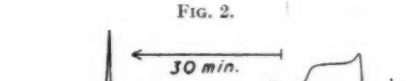

Fig. 1. *Ammonia chromatograms with mean linear concentration of silver nitrate,* 0·071 *mg. cm.*$^{-1}$; *column length,* 254·0 *cm.*; *carrier flow-rate,* 34·3—34·8 *cm.*^{3} *min.*$^{-1}$; *column temperature,* 17·4—19·8°; *sample size, cm.*^{3} (*N.T.P.*), *A,* 1·00; *B,* 1·50; *C,* 1·69; *D,* 2·00; *E,* 2·50; *F,* 3·00; *G,* 3·50. *Injection indicated by vertical stroke.*

Fig. 2. *Ammonia chromatograms with mean linear concentration of silver nitrate,* 0·196 *mg. cm.*$^{-1}$; *column length, cm., A,* 90·0; *B,* 171·0; *C,* 254·0; *carrier flow-rate,* 34·1—34·3 *cm.*^{3} *min.*$^{-1}$; *column temperature,* 17·7—20·3°; *sample size,* 2·50 *cm.*^{3} (*N.T.P.*). *Injection indicated by vertical stroke.*

Fig. 3.

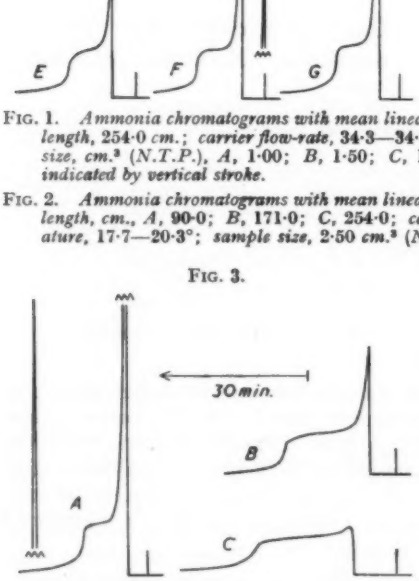

Fig. 3. *Ammonia chromatograms with mean linear concentration of silver nitrate, mg. cm.*$^{-1}$, *A,* 0·071; *B,* 0·134; *C,* 0·196; *column length,* 254·0 *cm.*; *carrier flow-rate,* 34·1—34·8 *cm.*^{3} *min.*$^{-1}$; *column temperature,* 18·8—19·8°, *sample size,* 4·00 *cm.*^{3} (*N.T.P.*). *Injection indicated by vertical stroke.*

is slow and extends over the passage of several samples, as is shown by a gradual approach of the chromatograms to reproducibility. A packing rich in silver nitrate gives reproducible results only after it has " matured " for a few days after passage of a few samples.

112 chromatograms were obtained with matured packings and typical examples are shown in Figs. 1—3. Fig. 1 shows the effect of sample size. For a given packing and column length, there is a reproducible critical sample size giving a plateau followed by a " tail " (Fig. 1*C*), while samples larger than the critical produce a peak superimposed on the front of the plateau. The height of the peak grows rapidly with increase in sample size, while the plateau changes little. Reduction of sample size below the critical causes the plateau to decay from both ends. Figs. 2 and 3 show that increase in column length and increase in silver nitrate concentration both cause the plateau to grow at the expense of the peak. Decrease in carrier flow-rate merely stretches the chromatogram in the direction of the time axis.

Discussion

Since the colour of a packing changes from white to pale mauve soon after preparation, it is uncertain whether the silver nitrate persists as such, and the salt in the column is therefore represented as AgZ. It is suggested that the absorption of ammonia by a new column is due to the formation of a stable ammine $AgZ(NH_3)_x$, while a matured column retards ammonia by the reaction

$$AgZ(NH_3)_x + yNH_3 \rightleftharpoons AgZ(NH_3)_{x+y}$$

for which the equilibrium ammonia pressure is p. A sample is injected at a pressure higher than p and moves rapidly through the column as a narrow zone (I), which continually loses ammonia to a slower-moving zone (II) in which ammonia is in equilibrium with $AgZ(NH_3)_x$ and $AgZ(NH_3)_{x+y}$ and therefore exerts pressure p. The emergence of zone I is recorded as a peak and that of zone II as a plateau. Let c = concentration of ammonia in fixed phase, c_1 = value of c corresponding to complete conversion of $AgZ(NH_3)_x$ into $AgZ(NH_3)_{x+y}$. Then $c = c_1$ immediately behind zone I and $c \not> c_1$ throughout zone II. If $c < c_1$ in any part of zone II, then that part moves faster than where $c = c_1$ and moves up to zone I. Thus $c = c_1$ throughout zone II. Following zone II there is a zone (III) in which the ammonia pressure is less than p and $c < c_1$, and whose emergence is recorded as a " tail."

Quantitative treatment of a chromatogram like Fig. 1*C* gives p and y. Such a chromatogram is obtained when zone I has just vanished upon reaching the end of the column. At this instant, zone II extends a distance L_1 * upwards from the end of the column. Apportionment by area measurements of the injected ammonia between the plateau and the tail gives the amount of ammonia emerging at partial pressure p, which can be found by applying the ideal-gas equation to the volume of gas escaping while the plateau is recorded. The amount of ammonia in both phases in zone II, excluding that in $AgZ(NH_3)_x$, is taken to be that producing the plateau. This is an approximation, since a small part of zone II degenerates into zone III while the plateau is recorded. The amount of ammonia in the fixed phase in zone II, excluding that in $AgZ(NH_3)_x$, is found by subtracting from the total the amount in the gas phase, found by applying the ideal-gas equation to the void volume in length L_1. Carman [4] reports the void volume to be 38% of total volume for randomly-packed, well-shaken spheres of equal size, but the packings were found to be more permeable to gas flow than the uncoated beads, and therefore their void volume is taken to be 50%. Since only a small fraction of the ammonia is in the gas phase, an error in the assumed void volume has little effect on the calculated amount of ammonia in the fixed phase. The amount of salt in zone II is found from L_1 and the density and composition of the packing.

L_1 is found from the emergence time t_L and final retention time t_s of the plateau (see Fig. 1*C*). If the pressure drop is low, so that the linear gas speed is nearly uniform through the column, and if the decay of the rear end of zone II is neglected, then the speed of the rear end is L/t_s, where L = length of packing, and L_1 is traversed in time t_L and has the value Lt_L/t_s. Where the pressure drop is appreciable, the effect of compressibility on gas speed has to be taken into account, by means of equations developed by Keulemans.[3] Combination of his equations (5) and (10) gives

$$t_g = Kp_o[(p_i/p_o)^3 - 1]/3\eta u_o^2,$$

where t_g = residence time of carrier gas, K = permeability of packing (assumed uniform), η = dynamic viscosity of carrier gas, u_o = linear speed of gas at column outlet, p_i = inlet

* Symbols used by Keulemans [3] are adopted here with slight modifications.

[4] Carman, " Chemical Constitution and Properties of Engineering Materials," Edward Arnold and Co., London, 1949, p. 28.

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pressure, p_o = outlet pressure. Since the speed of zone II is a constant fraction r of the carrier speed,

$$t_s = Kp_o[(p_i/p_o)^3 - 1]/3\eta u_o^2 r \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and

$$t_L = Kp_o[(p_L/p_o)^3 - 1]/3\eta u_o^2 r \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where p_L = pressure at distance L_1 from outlet, decay of zone II being neglected. From (1) and (2),

$$(p_L/p_o)^3 = 1 + t_L[(p_i/p_o)^3 - 1]/t_s \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Keulemans's equation (6) can be modified to

$$L_1/L = [(p_L/p_o)^2 - 1]/[(p_i p_o)^2 - 1] \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Equations (3) and (4) are used to find L_1 from measured values of t_L, t_s, p_i, p_o, and L.

Dissociation pressure and composition of ammine.

$AgNO_3$ *	Packing length (cm.)	Flow-rate ($cm.^3$ $min.^{-1}$)	Pressure drop (mm.)	Column temp.	10^3p (atm.)	y
0·071	254·0	34·8	304	19·6°	6·3	0·77
,,	254·0	34·3	303	19·2	6·2	0·74
0·134	254·0	33·8	203	20·0	5·7	0·53
0·168	257·9	34·9	309	17·0	5·5	0·53
0·196	254·0	34·0	228	18·6	5·1	0·45
,,	254·0	34·2	229	20·2	5·3	0·43
,,	254·0	34·3	230	19·3	5·3	0·45
,,	171·0	34·2	158	20·1	5·8	0·48
,,	171·0	16·2	78·1	20·5	6·2	0·51
,,	90·0	7·84	19·9	20·6	5·8	0·60

* Mean linear concentration of silver nitrate (mg. $cm.^{-1}$).

The Table shows values of p and y calculated from chromatograms including some which differ slightly from the type of Fig. 1*C*, allowance being made in ammonia apportionment for areas not belonging to the plateau. Mean values and standard deviations are: 10^3p, 5·7, 0·42 atm.; y, 0·50, 0·056. While the large standard deviations reflect the approximate nature of the calculations, p and y do not vary systematically with the controlled variables, except that the lean packing (0·071 mg. $cm.^{-1}$ of silver nitrate) gives high values for y, possibly because adsorption and solution play a larger rôle relative to ammine formation. These values are excluded from the calculation of the mean and standard deviation. The mean value of y shows the equation for ammine formation to be

$$AgZ(NH_3)_x + 0{\cdot}5NH_3 \rightleftharpoons AgZ(NH_3)_{x+0{\cdot}5}.$$

Other workers [1] have not observed the plateau. They have used concentrated solutions of silver salts and their peaks are probably lower than the corresponding plateaux, like the peak of Fig. 1*A*.

Experimental

Apparatus.—The gas-chromatographic apparatus was of conventional type, with glass columns of 6 mm. i.d., flow regulator, manometer, sample injector similar to Harrison's,[5] katharometer and bridge circuit (supplied by Messrs. Griffin and George Ltd., Wembley), recorder (Honeywell Brown, 3 mv f.s.d.), and soap-film flow-meter discharging to atmosphere. The recorder chart speed was 6 in. $hr.^{-1}$ and sensitivity [6] 52 ml. mv $mg.^{-1}$.

Solid Support.—Glass beads ("Ballotini," Grade 15, 0·10 mm. diam. and Grade 8a, 0·40 mm. diam., supplied by the English Glass Co. Ltd., Leicester) as purchased retained ammonia too strongly for use as a support; treatment with acid or alkali (but not with water) reduced the retentivity. The material used was boiled briefly with 30% sodium hydroxide solution, washed thoroughly with distilled water, and dried in an oven. When uncoated and when

[5] Harrison in "Vapour Phase Chromatography" (Desty, ed.), Butterworths Scientific Publications, London, 1957, p. 332.
[6] Johnson and Stross, *Analyt. Chem.*, 1958, **30**, 1586.

coated with the same proportion of benzyl cyanide as used in the test packings, it gave tailing ammonia peaks with low retention time.

Packings.—The packings were made by dissolving silver nitrate (M. and B. Laboratory Chemical, assay $\not<99{\cdot}8\%$) in benzyl cyanide (B.D.H. Laboratory Reagent), diluting with ethyl ether (Riedel-de Haën, Analytical Quality), making into a slurry with " Ballotini," Grade 15, and evaporating off the ether at room temperature with a stream of dry nitrogen. Dilution with ether caused the solutions to turn milky. The coarser beads could be coated without ether, and gave the same chromatograms as when ether was used.

Ammonia.—This was obtained by mixing concentrated solutions of ammonium nitrate and of sodium hydroxide, swept with nitrogen through calcium oxide desiccant, and condensed in a trap containing calcium oxide. The trap was evacuated while cold and left overnight at room temperature, after which the dry ammonia was condensed into an evacuated reservoir. Gas chromatography showed the ammonia to contain traces of impurities.

Carrier Gas.—Cylinder nitrogen, dried with phosphoric oxide, was used.

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University of Cape Town. [*Received, December 21st,* 1958.]

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408. *The Chemistry of the Triterpenes and Related Compounds. Part XXXV.* Some Non-acidic Constituents of* Polyporus pinicola, *Fr.*

By T. G. Halsall and G. C. Sayer.

Two new trimethyl-steroids, 21-hydroxylanosta-7 : 9(11)-24-trien-3-one and lanosta-7 : 9(11) : 24-triene-3β : 21-diol, have been isolated from the neutral extract of *Polyporus pinicola* Fr. Another component appears to be a mixture of ergost-7-en- and ergosta-7 : 22-dien-3β-ol.

Numerous publications describing the neutral constituents of the higher fungi have established that they include a complex mixture of sterols related to ergosterol.[1,2] In particular, Zellner and his co-workers have frequently recorded the presence of ergosterol and " ergosterol-like " compounds in the extracts of the sporophores of various Basidiomycetes. These sterol mixtures were difficult to separate and it is clear that in many cases the " ergosterol " was impure and inadequately characterised. Compounds other than ergosterol have also been reported.[3,4]

From *Polyporus pinicola* Hartmann and Zellner isolated a number of neutral substances with high melting points and also recorded the isolation of fungisterol as well as ergosterol.[5] It is likely, however, that their fungisterol was not pure. Fungisterol, now known to be ergost-7-en-3β-ol,[6] is also said to be a constituent of *Calocera viscosa*,[7] *Polyporus confluens* Fr.,[3] *P. sulphureus* (Bull) Fr.,[8] *Hydnum imbricatum* L.,[9] and *Geaster fimbriatus* Fr.[10] Ergosta-7 : 22-diene-3-one has been isolated from *Fomes fomentarius*.[11] Schmid and

* Part XXXIV, *J.*, 1959, 1877.

1 Cf. Rosethal, *Sitzungsber. Akad. Wiss. Wien*, IIb, 1922, **131**, 189.
2 Cf. Elsevier's " Encyclopaedia of Organic Chemistry," 1940, Vol. XIV; 1954 Vol. XIV S.
3 Fröschl and Zellner, *Monatsh.*, 1929, **53**—**54**, 146.
4 Sumi, *Chem. Zentr.*, 1931, I, 1773.
5 Hartmann and Zellner, *Monatsh.*, 1928, **50**, 193.
6 Wieland and Coutelle, *Annalen*, 1941, **548**, 270.
7 Fröschl and Zellner, *Monatsh.*, 1928, **50**, 201.
8 Zellner and Zikmunda, *ibid.*, 1930, **56**, 200.
9 Lukacs and Zellner, *ibid.*, 1933, **62**, 214.
10 Ruthner and Zellner, *ibid.*, 1935, **66**, 76.
11 Arthur, Halsall, and Smith, *J.*, 1958, 2603.

Czerny [12,13] recently described the isolation of a sterol mixture, said to be ergosterol and fungisterol, from the light petroleum extract of *P. pinicola*, and also of an oxo-alcohol, m. p. 116°, $[\alpha]_D$ +71°, $\lambda_{max.}$ 2360, 2450, and 2520 Å (ε 5400, 6000, and 4200).

Continuing our systematic examination of the wood-rotting fungi we have now examined some of the neutral constituents of *Polyporus pinicola* Fr. The first constituent isolated was a small amount of material with the melting point of ergosterol but with a much smaller negative rotation and a lower intensity of absorption at 2820 Å. The main component (A) isolated had m. p. 157—159° and $[\alpha]_D$ −13° and showed no selective ultraviolet absorption. Its analysis agreed with the formula $C_{28}H_{46(48)}O$. Its constants resemble those reported for " anasterol," a substance isolated as its benzoate by Wieland and Gough [14] from the mother-liquors from the crystallisation of impure ergosteryl benzoate. The constants of component A and its derivatives are compared with those of ergosta-7 : 22-dien-3β-ol and the dihydro-derivative, fungisterol (cf. Table). Component A may be a mixture of ergosta-7 : 22-dien- and ergost-7-en-3β-ol.

Another constituent was isolated as its acetate, the ultraviolet absorption of which indicated that it contained the 7 : 9(11)-diene system of a trimethyl-steroid. Hydrolysis gave a ketol, reduction of which yielded lanosta-7 : 9(11)-24-triene-3β : 21-diol (III) identical both with an authentic sample prepared from pinicolic acid A (I) and with a further constituent of the neutral material from *P. pinicola*.

	Alcohol		Acetate		Benzoate	
	M. p.	$[\alpha]_D$	M. p.	$[\alpha]_D$	M. p.	$[\alpha]_D$
Ergosta-7 : 22-dien-3β-ol	176° [a]	−19°	178—180° [a]	−19°	200°	−10°
Component A	157—159	−13	167—168	−6	189—192	−2
Ergost-7-en-3β-ol (fungisterol) ...	148 [b]	−2	157—159 [b]	−4	180·5 [b]	+2
" Anasterol "	157—159 [c]	−8	—	—	180—182 [c]	−14

[a] Barton and Cox, *J.*, 1948, 1354. [b] *Idem, ibid.*, p. 783. [c] Ref. 14.

The conversion of pinicolic acid A (I) into the trienediol (III) was carried out by chromic acid oxidation of its methyl ester to methyl 3 : 7-dioxolanosta-8 : 24-dien-21-oate (II) which was reduced with lithium aluminium hydride to the intermediate allylic triol. This was dehydrated with acetic anhydride, and the product hydrolysed to the diol (III).

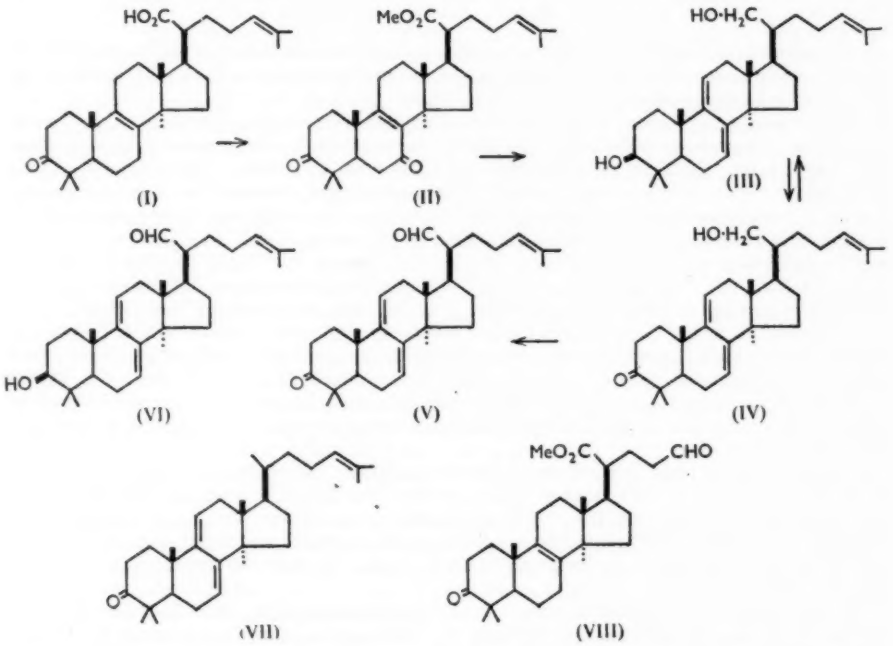
Of the two possible structures (IV and VI) initially considered for the ketol the latter was excluded because oxidation of the ketol gave the keto-aldehyde (V) which had infrared bands at 2700 and 1725 $cm.^{-1}$ typical of an aldehyde group and absent from the spectrum of its precursor. The change in rotation on reduction of the carbonyl group in the ketol (IV) (ΔM_D + 72°) corresponds well with that occurring on reduction of agnosterone (VII) (ΔM_D + 71°). The ketol was obtained by Oppenauer oxidation of the diol (III) prepared from pinicolic acid A (I).

These results differ somewhat from those obtained in a preliminary examination carried out some time ago on a small amount of fungus when two products were obtained in addition to crude ergosterol.[15] The first was an oxo-alcohol, m. p. 114—117°, $[\alpha]_D$ +68·5°, $\lambda_{max.}$ 2360 and 2430, inflexion 2510 Å (ε 4000, 4500, and 3000). These constants are very similar to those of the oxo-alcohol obtained by Schmid and Czerny [13] and the two materials are almost certainly identical. These constants indicate a mixture of 21-hydroxylanost-8 : 24-dien-3-one (75%) and the corresponding dehydro-derivative [7 : 9(11)-diene (IV)]. Reduction of this mixture with sodium borohydride gave a mixture of diols, $[\alpha]_D$ +57°, m. p. 189—192°, undepressed * on admixture with pure lanosta-8 : 24-diene-3β : 21-diol, m. p. 189—192°, $[\alpha]_D$ +57°, prepared by reduction of pinicolic acid A with

* One feature of this field of chemistry is the absence of melting-point depression when a significant amount of a 7 : 9(11)-diene is mixed with the parent 8-ene.

[12] Schmid and Czerny, *Sci. Pharm.*, 1953, **21**, 258.
[13] *Idem, Monatsh.*, 1954, **85**, 1307.
[14] Wieland and Gough, *Annalen*, 1930, **482**, 36.
[15] Guider, Ph.D. Thesis, Manchester, 1954.

lithium aluminium hydride.[16] The second product, m. p. 189—192°, $[\alpha]_D$ +60°, $\lambda_{max.}$ 2360 and 2430, inflexion 2510 Å (ε 8500, 9700, and 6500), was apparently a mixture of the corresponding diol and its dehydro-derivative [7 : 9(11)-diene) (III)]. It is probable that the percentage of the trimethyl-steroid fraction in the oxidised 7 : 9(11)-diene form differs



in different samples of fungus, possibly varying with the conditions of growth and time of collection.

The preparation of a trisnor-derivative (VIII) of pinicolic acid A (I) needed as a reference compound is described below.

Experimental

M. p.s were determined on a Kofler block and are corrected. Rotations were determined for chloroform solution at room temperature. Alumina for chromatography was usually alumina (activity II) which had been deactivated with 5% of 10% aqueous acetic acid. Light petroleum refers to the fraction with b. p. 60—80°. Infrared spectra were determined for CS_2 solution unless otherwise stated.

Extraction of Polyporus pinicola *and Isolation of the Neutral Fraction.*—The fungus (9·5 kg.) extracted with alcohol, and the extract separated into acidic and neutral fractions in the usual way. An ethereal solution of the neutral fraction was repeatedly extracted with cold 5% aqueous potassium hydroxide and then kept with cold 10% methanolic potassium hydroxide for several days after which it was again separated into neutral and acidic fractions. The neutral fraction (93·5 g.) in methanol (500 c.c.) was heated under reflux for 24 hr. with 1% methanolic potassium hydroxide (2 l.). The solution was cooled to 20° and diluted with ether (2 l.) and water (2 l.). The ethereal layer was separated and the aqueous layer twice more extracted with ether (2 l.). Working up the ethereal extracts in the usual manner gave the non-saponifiable neutral fraction as a dark-brown gum (86·5 g.).

Chromatographic Separation of the Neutral Fraction.—This fraction (86 g.) was adsorbed

[16] Guider, Halsall, and Jones, *J.*, 1954, 4471.

from light petroleum–benzene (3 : 1; 1·5 l.) on alumina (2 kg.; deactivated with 10% of 10% acetic acid) and eluted as shown:

Fraction	Eluent	Vol. (l.)	Wt. (g.)	Appearance	$\lambda_{max.}$ (principal)
1	Light petroleum	18	53·5	Waxy brown solid	2430, 2820 Å
2	Benzene	12	13	Pale brown solid	2430 Å
3	Ether	15	19·8	Brown gum	—

Examination of fraction 1. This fraction crystallised from methanol as plates (fraction 1A) (6·78 g.), m. p. 157—163°. Evaporation of the mother-liquor gave a dark gum (fraction 1B) (46 g.) which slowly gave a crystalline mass (needles).

(i) Fraction 1A. Repeated recrystallisation of this fraction from methanol gave a small amount of plates, m. p. 163—166°, undepressed on admixture with ergosterol monohydrate, $[\alpha]_D$ −18° (*c* 1·15), $\lambda_{max.}$ 2710, 2810, and 2930 Å (ε 6300, 6600, and 3700). The residue (6 g.) from the combined mother-liquors from these crystallisations was examined by chromatography, 1 g. of it being adsorbed from light petroleum–benzene (1 : 1; 85 c.c.) on alumina (100 g.). Elution with benzene (600 c.c.) gave compound A (185 mg.), m. p. 157—159° (needles from methanol; leaflets from acetone), $[\alpha]_D$ −13° (*c* 1·04) (Found: C, 82·45; H, 11·85. Calc. for $C_{28}H_{46}O,1{\cdot}5CH_3{\cdot}OH$: C, 82·55; H, 11·65%). Compound A showed no significant ultraviolet light absorption but infrared max. (in Nujol) at 3350, 1640, 870, 845, 827, and 795 cm.$^{-1}$.

Compound A (80 mg.) in pyridine (1·5 c.c.) was acetylated with acetic anhydride (0·5 c.c.) at 20° for 24 hr. Isolation with ether gave compound A acetate, m. p. 167—168° (needles from methanol and acetone), $[\alpha]_D$ −6° (*c* 1·02) (Found: C, 81·65; H, 10·9. Calc. for $C_{30}H_{48}O_2$: C, 81·75; H, 11·0%), $\nu_{max.}$ (in Nujol) 1730, 1640, 840, 825, and 795 cm.$^{-1}$. Hydrolysis of the acetate with methanolic potassium hydroxide gave back compound A, m. p. and mixed m. p. 156—158°.

Compound A (75 mg.) in pyridine (1·5 c.c.) was treated with benzoyl chloride (0·5 c.c.) at 20° for 24 hr. Isolation with ether yielded a product (105 mg.) which was adsorbed from light petroleum (25 c.c.) on alumina (10 g.). Elution with light petroleum (50 c.c.) gave compound A benzoate, m. p. 189—192° (plates from methanol–ethyl acetate and ethyl acetate), $[\alpha]_D$ −2° (*c* 1·03) (Found: C, 83·65; H, 10·4. Calc. for $C_{35}H_{50}O_2$: C, 83·6; H, 10·0%), $\nu_{max.}$ 1710, 840, 825, and 795 cm.$^{-1}$.

(ii) Isolation of 21-hydroxylanosta-7 : 9(11) : 24-trien-3-one (IV) from fraction 1B. This fraction (1 g.) in light petroleum–benzene (3 : 1; 100 c.c.) was adsorbed on alumina (100 g.). Elution with light petroleum–benzene (1 : 1; 300 c.c.) gave a gum (265 mg.) which slowly crystallised in contact with methanol to give the impure ketol, m. p. 114—117°, $\lambda_{max.}$ 2430 Å (ε 8900). Only small and impure quantities of crystalline material were obtained from other fractions, some of which showed low intensity maxima at 2430 and 2810 Å.

The impure ketol (240 mg.) in pyridine (5 c.c.) was treated with acetic anhydride (1·5 c.c.) at 20° for 24 hr. Isolation with ether gave a product (230 mg.) which was adsorbed from light petroleum (25 c.c.) on alumina (20 g.). Elution with light petroleum–benzene (3 : 1; 350 c.c.) gave 21-*acetoxylanosta*-7 : 9(11) : 24-*trien*-3-*one*, m. p. 111—113° (from methanol and aqueous methanol), $[\alpha]_D$ +81° (*c* 1·08) (Found: C, 79·65; H, 9·85. $C_{32}H_{48}O_3$ requires C, 79·95; H, 10·1%), $\lambda_{max.}$ 2360, 2430, and 2510 Å (ε 15,000, 16,800, and 11,400).

21-Acetoxylanosta-7 : 9(11) : 24-trien-3-one (100 mg.) in methanol (10 c.c.) was treated with 10% methanolic potassium hydroxide (10 c.c.) at 20° overnight. Isolation with ether gave the ketol as a gum which was adsorbed from light petroleum (20 c.c.) on alumina (10 g.). Elution with light petroleum–benzene (1 : 1; 150 c.c.) gave 21-*hydroxylanosta*-7 : 9(11) : 24-*trien*-3-*one* as needles (from dilute methanol or ethanol), m. p. 119—121°, $[\alpha]_D$ +56° (*c* 0·97) (Found: C, 82·4; H, 10·4. $C_{30}H_{46}O_2$ requires C, 82·1; H, 10·6%), $\lambda_{max.}$ 2360, 2430, and 2510 Å (ε 10,400, 12,300, and 7800), $\nu_{max.}$ 1710 and 3600 cm.$^{-1}$.

The ketol (50 mg.) in purified dioxan (5 c.c.) was reduced with sodium borohydride (15 mg.) in aqueous dioxan (1 : 1; 5 c.c.) at 20° for 1 hr. After dilution with water isolation with ether yielded a product which was adsorbed from benzene (5 c.c.) on alumina (10 g.). Elution with benzene–ether (9 : 1; 50 c.c.) gave lanosta-7 : 9(11) : 24-triene-3β : 21-diol, m. p. 194—196° (from methanol), identical with an authentic sample of the diol (see below).

The ketol (80 mg.) in acetone (20 c.c.) was oxidised with chromic acid in the usual manner.[17] Isolation with ether gave a product which was adsorbed from light petroleum (7 c.c.) on alumina

[17] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2555.

(10 g.). Elution with light petroleum–benzene (9 : 1; 100 c.c.) gave lanosta-7 : 9(11) : 24-triene-3 : 21-dione, m. p. 141—142° (from methanol), identical with an authentic sample (see below).

Examination of fraction 2. This fraction (13 g.) crystallised from methanol as needles (fraction 2A) (3·85 g.), m. p. 185—190°. Evaporation of the mother-liquors gave a resinous solid (fraction 2B).

(*a*) Isolation of lanosta-7 : 9(11) : 24-triene-3β : 21-diol (III). Fraction 2A was adsorbed from benzene (200 c.c.) on alumina (400 g.). Elution with benzene–ether (9 : 1; 2 l.) gave *lanosta*-7 : 9(11) : 24-*triene*-3β : 21-*diol*, which was obtained as needles (from methanol), m. p. 194—197°, $[\alpha]_D$ +72° (*c* 1·06) (Found: C, 81·5; H, 11·15. $C_{30}H_{48}O_2$ requires C, 81·75; H, 11·0%), $\lambda_{max.}$ 2360, 2430, and 2510 Å (ε 12,900, 15,300, and 10,300). The diol (200 mg.) was acetylated in pyridine (5·5 c.c.) with acetic anhydride (2·5 c.c.) at 20° for 24 hr. to give 3β : 21-*diacetoxylanosta*-7 : 9(11) : 24-*triene* as needles (from methanol), m. p. 122°, $[\alpha]_D$ +73° (*c* 0·8) (Found: C, 78·0; H, 10·0. $C_{34}H_{52}O_4$ requires C, 77·8; H, 10·0%).

(*b*) Examination of fraction 2B. Fraction 2B (1 g.) in benzene was adsorbed on alumina (100 g.). Elution with benzene–ether (3 : 1; 500 c.c.) gave several fractions (350 mg.) which crystallised from methanol as needles, having m. p.s within the range 175—190°. These fractions were not pure and contained up to 25% of conjugated dienes.

Examination of fraction 3. Chromatography of this fraction did not yield any crystalline fractions.

Oxidation of Lanosta-7 : 9(11) : 24-*triene*-3β : 21-*diol*.—The diol (300 mg.) in acetone (100 c.c.) was oxidised with chromic acid in the usual manner. Isolation with ether gave a product which was adsorbed from light petroleum (35 c.c.) on alumina (20 g.). Elution with light petroleum–benzene (9 : 1; 400 c.c.) gave *lanosta*-7 : 9(11) : 24-*triene*-3 : 21-*dione* (V) (175 mg.) as stout needles (from methanol), m. p. 142—143°, $[\alpha]_D$ +49° (*c* 0·99) (Found: C, 82·7; H, 9·9. $C_{30}H_{44}O_2$ requires C, 82·5; H, 10·15%), $\lambda_{max.}$ at 2360, 2430, and 2510 Å (ε 15,300, 17,200, and 11,500), $\nu_{max.}$ 2700, 1725, and 1710 cm.$^{-1}$.

Oppenauer Oxidation of Lanosta-7 : 9(11)-24-*triene*-3β : 21-*diol*.—The diol (200 mg.) and aluminium *tert.*-butoxide (106 mg.) in dioxan (15 c.c.) were heated to the b. p., treated with *cyclo*hexanone (5 c.c.), and heated under reflux for 24 hr. After dilution with water and acidification, isolation with ether yielded a gum which was adsorbed from light petroleum–benzene (2 : 1; 40 c.c.) on alumina (20 g.).

Elution with light petroleum–benzene (2 : 1; 350 c.c.) yielded a gum (100 mg.) which was dissolved in pyridine (2 c.c.) and acetylated with acetic anhydride (0·6 c.c.). Isolation with ether afforded a product which was adsorbed on alumina (10 g.) from light petroleum (10 c.c.). Elution with light petroleum–benzene (3 : 1; 150 c.c.) gave 21-acetoxylanosta-7 : 9(11) : 24-trien-3-one as needles (from methanol), m. p. 112—114°, $[\alpha]_D$ +81° (*c* 1·0), identical with that prepared from the ketol from the fungus.

Conversion of Methyl Pinicolate A into Lanosta-7 : 9(11) : 24-*triene*-3β : 21-*diol* (III).—Methyl pinicolate A (500 mg.) in acetic acid (10 c.c.) was treated with recrystallised chromic acid (150 mg.; 2·1 mol. with respect to oxygen) in acetic acid (10 c.c.) at 85° for 10 min. Dilution with water and isolation with ether yielded a product ($\lambda_{max.}$ 2520 Å) which was adsorbed from light petroleum (30 c.c.) on alumina (50 g.). Elution with light petroleum–benzene (2 : 1; 300 c.c.) gave unchanged methyl pinicolate A (200 mg.), m. p. 119—121° (from methanol).

Elution with benzene (400 c.c.) afforded a gum (250 mg.) which slowly formed a sticky solid which was extremely soluble in organic solvents. It showed maximal light absorption at 2520 Å (ε 9800) indicative of the presence of methyl 3 : 7-dioxolanosta-8 : 24-dien-21-oate.

The crude methyl 3 : 7-dioxolanosta-8 : 24-dien-21-oate (250 mg.) described above in ether (50 c.c.) was heated under reflux with lithium aluminium hydride (520 mg.) for 3 hr. The excess of reagent was destroyed with ethyl acetate, and the complex decomposed with dilute hydrochloric acid. Isolation with ether gave a solid which was heated under reflux with acetic anhydride (30 c.c.) for 1 hr. Dilution with water and extraction with ether afforded a product which was heated under reflux with 10% methanolic potassium hydroxide (35 c.c.) for 30 min. Isolation with ether gave the crude diol which was adsorbed from benzene (25 c.c.) on alumina (20 g.). Elution with light petroleum–benzene (9 : 1; 400 c.c.) gave *lanosta*-7 : 9(11) : 24-*triene*-3β : 21-*diol* (145 mg.) which crystallised from methanol as needles, m. p. 196—197°, identical with the diol from the fungus.

Lanosta-8 : 24-*diene*-3β : 21-*diol* [with Miss J. M. Guider].—Methyl pinicolate A (150 mg.)

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in ether (50 c.c.) was heated under reflux with lithium aluminium hydride (100 mg.) for 1 hr. After decomposition of the excess of hydride, the complex was decomposed with an aqueous solution of tartaric acid. Extraction with ether gave *lanosta*-8 : 24-*diene*-3β : 21-*diol*, m. p. 189—192° (needles from methanol and from acetone), $[\alpha]_D$ +57° (*c* 0·94 in pyridine) (Found: C, 81·6; H, 11·3. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%).

Conversion of Methyl Pinicolate A into Methyl 3 : 24-*Dioxotrisnorlanost*-8-*en*-21-*oate*.—Methyl pinicolate A (280 mg.) in dry ether (5 c.c.) was treated with osmium tetroxide (160 mg.) at 20° for 3 days. The solution was evaporated to dryness under reduced pressure and the residue in chloroform (50 c.c.) was shaken with a solution of mannitol (2·5 g.) and potassium hydroxide (2·5 g.) in water (50 c.c.) for 24 hr. Isolation with chloroform gave the crude diol as a gum (260 mg.) which was dissolved in ethanol (50 c.c.) and treated with a solution of sodium metaperiodate (260 mg.) in water (5 c.c.). A little water was added to clarify the solution which was kept at 20° for 2 days. Isolation with ether afforded a product which was adsorbed from light petroleum–benzene (9 : 1; 55 c.c.) on alumina (15 g.). Elution with light petroleum–benzene (1 : 1; 400 c.c.) gave a gum (65 mg.) which crystallised from methanol to give *methyl* 3 : 24-*dioxotrisnorlanost*-8-*en*-21-*oate* as needles, m. p. 138—139°, $[\alpha]_D$ +67° (*c* 1·19) (Found: C, 76·15; H, 9·65. $C_{28}H_{42}O_4$ requires C, 75·95; H, 9·55%), $\nu_{max.}$ 2700, 1730, and 1708 cm.$^{-1}$.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, January 13th*, 1959.]

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409. *The Chemistry of the Triterpenes and Related Compounds. Part XXXVI.* Some Constituents of* Trametes odorata *(Wulf.) Fr.*

By T. G. HALSALL, R. HODGES, and G. C. SAYER.

3β-Hydroxylanosta-8 : 24-dien-21-oic acid has been isolated as its methyl ester from the sporophores of the fungus *Trametes odorata*. Three other acids have also been isolated as their methyl esters.

IN continuation of our investigations of the wood-rotting fungi we have made a preliminary examination of the constituents of *Trametes odorata* (Wulf.) Fr. found on fir and pine trees in Norway and Austria. The constituents were first examined by Gruber and Proske [1] in 1950. From a cold ether extract of the dry pulverised sporophores of fungus they isolated " trametenolic acid," m. p. 259—261°, $[\alpha]_D$ +47° in methanol. They suggested a formula of $C_{30}H_{48}O_3$ or $C_{31}H_{50}O_3$. The acid was characterised as a secondary hydroxy-acid with two double bonds and was converted [2] by standard procedures into the parent hydrocarbon " trametene." The chief products of dehydrogenation were reported [3] to be 1 : 2 : 5 : 6-tetramethylnaphthalene and 1 : 2 : 7 : 8-tetramethylphenanthrene. These results suggest that trametenolic acid is a tetracyclic triterpene although the dehydrogenation products are unusual.

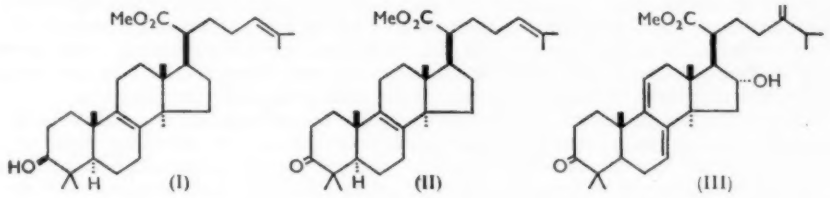
For our investigation a small amount (500 g.) of *Trametes odorata* was available. It was extracted first with ether and then with alcohol, approximately by the procedure of Gruber and Proske [1] in the hope of isolating trametenolic acid. The extracts were separated into acidic and neutral fractions. The latter were very small and not investigated further. The two acidic fractions were methylated with diazomethane, and the resulting esters separated by alumina chromatography.

The main component of the esters resulting from the ether extract was methyl 3β-hydroxylanosta-8 : 24-dien-21-oate (I) previously obtained by reduction of the corresponding keto-compound, methyl pinicolate [4] (II), with sodium borohydride. From a comparison of the constants of the hydroxy-ester (I) and its derivatives it does not appear to be methyl trametenolate (cf. Table, p. 2040). For comparison with the trametenolic acid

* Part XXXV, preceding paper.

[1] Gruber and Proske, *Monatsh.*, 1950, **81**, 837.
[2] *Idem, ibid.*, p. 1024.
[3] *Idem, ibid.*, 1951, **82**, 255.
[4] Guider, Halsall, and Jones, *J.*, 1954, 4471.

of Gruber and Proske the acid from ester (I) had to be prepared. However, the methyl ester, like methyl pinicolate A,[4] was not hydrolysed by boiling methanolic potassium hydroxide in 24 hours. To bring about hydrolysis of the esters (I) and (II) it was necessary to use boiling diethylene glycol as solvent. In contrast, methyl trametenolate is hydrolysed [1] under the milder conditions, as is also methyl polyporenate C (III).[5] The greater ease with which the ester group of methyl polyporenate C is hydrolysed may be due to the presence of the 16α-hydroxyl group. Adjacent hydroxyl groups can, if suitably placed, facilitate ester hydrolysis.[6]



In addition to methyl 3β-hydroxylanosta-8 : 24-dien-21-oate three other esters (ester A; m. p. 159—65°, $[\alpha]_D$ +49°; ester B, m. p. 152—153°, $[\alpha]_D$ +66°; ester C, m. p. 197—199°) have so far been isolated, but owing to the small amounts available they have not yet been investigated in detail. Most is known about ester B which has the formula $C_{32}H_{48}O_6$ or $C_{33}H_{50}O_6$ and appears to be the dimethyl ester of a C_{30} or C_{31} hydroxyketodicarboxylic acid. Its ultraviolet spectrum has a broad band at 2130 Å (ε 16,600), which suggests the presence of an αβ-unsaturated ester group (the true maximum due to such a group will be at a longer wavelength after allowance for end-absorption of isolated double bonds), and a low-intensity band at 2750—2800 Å suggestive of an isolated carbonyl group although the intensity (ε 120) is rather higher than that usually associated with ketones. The infrared spectrum (in Nujol) had a band due to a hydroxyl group and a very broad band in the carbonyl region with two peaks (1709 and 1722 cm.$^{-1}$; the former slightly more intense). There was also a band of moderate intensity at 1650 cm.$^{-1}$. These bands are consistent with a keto-group in a six-membered ring, an isolated ester group, and an αβ-unsaturated ester group. The keto-group is unreactive since ester B does not react with Girard's reagent or with sodium borohydride. Oxidation of ester B gave a compound, whose analysis indicated that it had two hydrogen atoms less than the starting material and hence that one hydroxyl group had been oxidised. The oxidation product had no band due to a hydroxyl group but bands at 1735 and 1710 (very broad) cm.$^{-1}$ (in carbon disulphide).

Alcoholic extracts of the fungus were intensely coloured by a pigment which was deposited from concentrated solutions as an amorphous reddish-brown powder and for which the name "trametin" is provisionally proposed. It does not contain nitrogen and hence differs from cinnabarin (polystictin) from *Trametes cinnabarina* and *Coriolus sangineus*.[7]

Experimental

The general experimental conditions described in Part XXXV apply also to this paper.

Extraction of T. odorata (*Wulf.*) *Fr.*—The chopped air-dried fungus (500 g.) was suspended in boiling ether for 24 hr. The ether was decanted and the fungus re-extracted thrice more in the same manner. From each extract a reddish-yellow solid (5·24; 2·12, 2·87, and 1·17 g.) was obtained on evaporation.

The residual fungus was extracted with cold alcohol for 1 month. The red-black extract

[5] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2548.
[6] Cf. Henbest and Lovell, *J.*, 1957, 1965.
[7] Cf. Cavill and Tetaz, *Chem. and Ind.*, 1956, 986.

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was decanted, filtered, and evaporated under reduced pressure to 500 c.c. The extract was then kept at 20° for a few days. During this period *ca.* 2 g. of an amorphous orange-brown pigment were deposited. It was filtered off and washed with light petroleum. It was then suspended successively in boiling light petroleum for 15 min. and in boiling ether for 15 min., filtered off, and dried. The substance provisionally called " trametin " darkened but did not melt when heated to 300° (Found: C, 54·75; H, 5·4%; N, 0). It was insoluble in most solvents except alcohol and acetone. The red colour of dilute solutions was intensified by addition of hydrochloric acid, but changed to a dark green in cold alcoholic alkali. It had $\lambda_{max.}$ (in 95% ethanol) 2300, 2760, and 4310 Å, shoulders at 4600 and 4950 Å. The minimum $E^{1\%}_{1\,cm.}$ values at 2670 and 4310 Å are 204 and 186. $\nu_{max.}$ (in Nujol) were at 3310 (broad) (OH), 1630 and 1580 cm.$^{-1}$.

Examination of the Ether Extract.—The residue from the first extract was dissolved in 1 : 1 methanol–ether (1 l.) and extracted with 10% potassium hydroxide solution. The neutral fraction (420 mg.) was obtained from the ethereal layer, and the acidic fraction was isolated from the aqueous phase by acidification with acetic acid and ether-extraction.

The acidic fraction was methylated with an excess of ethereal diazomethane, and the resulting mixed methyl esters (4·8 g.) were adsorbed from benzene (60 c.c.) on alumina (activity I—II) (300 g.) and eluted with the following solvents: benzene (0·5 l.), fraction 1 (0·51 g.), yellow viscous oil; benzene–ether (9 : 1) (4 l.), fraction 2 (1·05 g.), solid; benzene–ether (3 : 1) (3 l.), fraction 3 (0·33 g.), gum; 1 : 1 benzene–ether (1 l.), fraction 4 (0·68 g.) gum; ether (2 l.), fraction 5 (0·14 g.), yellow gum.

Fractions 1 and 5 did not crystallise and were not investigated further.

Fraction 2 was acetylated in pyridine (20 c.c.) with acetic anhydride (10 c.c.) at 20° for 24 hr. Isolation with ether yielded a product which crystallised from methanol as stout needles (920 mg.), m. p. 133—137°. These were adsorbed from light petroleum (30 c.c.) on alumina (85 g.). Elution with light petroleum–benzene (3 : 1; 400 c.c.) gave methyl 3β-acetoxylanosta-8 : 24-dien-21-oate as needles (from methanol), m. p. and mixed m. p. 147—149°, $[\alpha]_D$ +63° (*c.* 0·98) (Found: C, 77·2; H, 10·3. Calc. for $C_{33}H_{52}O_4$: C, 77·3; H, 10·2%). The compound showed no significant ultraviolet absorption. The methyl ester acetate (820 mg.) in methanol (100 c.c.) was hydrolysed overnight with 10% methanolic potassium hydroxide (100 c.c.) at 20°. Isolation with ether afforded a gum which gelatinised in contact with methanol. It was adsorbed from benzene (30 c.c.) on alumina (80 g.) and eluted with benzene (300 c.c.) to give methyl 3β-hydroxylanosta-8 : 24-dien-21-oate as needles (from propan-2-ol), m. p. 132—135°, $[\alpha]_D$ +52° (*c* 0·99) (Found: C, 78·85; H, 10·8. Calc. for $C_{31}H_{50}O_3$: C, 79·1; H, 10·7%). Oxidation of the hydroxy-ester (470 m.g.) in acetone (100 c.c.) in the usual manner [8] gave methyl pinicolate, m. p. 119—120°.

Hydrolysis of Methyl 3β-Hydroxylanosta-8 : 24-dien-21-oate.—(*a*) The hydroxy-ester (500 mg.) was heated under reflux with 10% methanolic potassium hydroxide (100 c.c.) for 24 hr. Dilution with water and extraction with ether yielded unchanged ester (465 mg.).

(*b*) The hydroxy-ester (500 m.g.) in diethylene glycol (25 c.c.) and potassium hydroxide (0·4 g.) were heated under reflux for 2 hr. After acidification with acetic acid and dilution with water ether-extraction afforded a brown gum which was adsorbed from benzene (20 c.c.) on alumina (50 g.; 10% deactivated). Elution with ether (500 c.c.) gave *3β-hydroxylanosta-8 : 24-dien-21-oic acid* as needles (from acetone and propan-2-ol), m. p. 253—258°, $[\alpha]_D$ +43° (*c* 0·94 in pyridine) (Found: C, 79·0; H, 10·45. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%). Hydrolysis of methyl pinicolate A under the same conditions afforded pinicolic acid A.

The hydroxy-acid (200 mg.) in pyridine (5 c.c.) was treated with acetic anhydride (2 c.c.) for 24 hr. at 20°. Isolation with ether gave *3β-acetoxylanosta-8 : 24-dien-21-oic acid* as needles (from dilute acetone), m. p. 240—244° (decomp., sublimes 225°), $[\alpha]_D$ +48 (*c* 1·3 in pyridine) (Found: C, 76·6; H, 10·2. $C_{32}H_{50}O_4$ requires C, 77·05; H, 10·1%).

Fractions 3 and 4 from the Ether Extract.—These fractions (1·0 g.) were combined and adsorbed from benzene (25 c.c.) on undeactivated alumina (80 g.). Elution with benzene–ether (1 : 1; 900 c.c.) gave ester A (probably a mixture of hydroxy-esters) as a gum (650 mg.) which crystallised from dilute ethanol and methanol as needles, m. p. 159—165°, $[\alpha]_D$ +49° (*c.* 0·73), $\lambda_{max.}$ 2350, 2430, and 2570 Å [intensity indicating the presence of *ca.* 9% of 7 : 9(11)-diene], $\nu_{max.}$ (in Nujol) 3440, 1720, 1675, 885, 845, and 820 cm.$^{-1}$.

Examination of the Alcohol Extract of the Fungus.—The concentrated alcohol extract was diluted with ether (500 c.c.) and extracted with potassium hydroxide solution. The colour of the extract immediately changed from red-black to green-black. The alkaline layer was

separated and extracted further with ether (500 c.c.). From the combined ethereal extracts a neutral fraction (0·34 g.) was obtained. Acidification of the alkaline phase with acetic acid produced a gelatinous suspension from which the acidic fraction (6·3 g.) was extracted (with difficulty) by three extractions with ether (1½ l.).

The acidic fraction was suspended in acetone (150 c.c.) and methylated with an excess of ethereal diazomethane. The resulting mixed methyl esters (4 g.) were adsorbed from benzene (200 c.c.) on alumina (250 g.; 10% deactivated). Elution with benzene (2 l.) gave a yellowish solid (2·3 g.) (fraction 1). Elution with benzene–ether (1 : 1; 2 l.) gave a yellow gum (1·3 g.) (fraction 2).

Examination of Fraction 1 *from the Alcohol Extract.*—This fraction was adsorbed from benzene (150 c.c.) on alumina (150 g.) and eluted as follows: benzene (600 c.c.), oil (200 mg.) (fraction 1); benzene–ether (9 : 1) (400 c.c.), yellow oil (540 mg.) (fraction 2); benzene–ether (9 : 1) (3·5 l.), solid (1·15 g.), m. p. 143—151° (fraction 3); benzene–ether (3 : 1) (100 c.c.), solid (30 mg.), m. p. 130—138° (fraction 4); benzene–ether (3 : 1) (100 c.c.), solid (20 mg.), 137—148° (fraction 5); benzene–ether (3 : 1) (100 c.c.), solid (20 mg.), m. p. 133—160° (fraction 6); benzene–ether (1 : 1) (100 c.c.), solid (30 mg.), m. p. 176—178° (fraction 7); and benzene–ether (1 : 1) (100 c.c.), solid (40 mg.), m. p. 182—187° (fraction 8).

Fractions 1 and 2 (740 mg.) were combined and adsorbed from light petroleum (50 c.c.) on alumina (60 g.). Elution with light petroleum–benzene (3 : 2; 200 c.c.) and benzene (200 c.c.) afforded small quantities of impure crystalline material, m. p. 135—155° and 129—139° respectively.

Fraction 3 (1·15 g.) was recrystallised several times from methanol to yield *ester B* as needles, m. p. 149—152°, $[\alpha]_D$ +66° (*c* 1·13) (Found: C, 72·45; H, 9·55. $C_{32}H_{48}O_6$ requires C, 72·7; H, 9·15. $C_{33}H_{50}O_6$ requires C, 73·05; H, 9·3%), $\lambda_{max.}$ (broad) at 2130 and 2750—2800 Å (ε 16,600 and 120), $\nu_{max.}$ (in Nujol) 3450, 1720, and 1708 (broad band with two maxima of approx. equal intensity), 1650, 860, and 830 cm.$^{-1}$.

Fraction 8 (40 mg.) crystallised from methanol to give ester C as needles, m. p. 197—199°. This substance showed no significant ultraviolet absorption. $\nu_{max.}$ (in Nujol) were at 3300, 1720, 1708, 1650, 900, 860, and 830 cm.$^{-1}$.

Treatment of Ester B with Girard's Reagent T.—The ester (770 mg.) in ethanol (50 c.c.) containing acetic acid (0·96 c.c.) was heated under reflux with Girard's reagent T (720 mg.) for 1 hr. The cooled mixture was poured into a solution of sodium carbonate (770 mg.) in ice-water. Extraction with ether yielded a solid which was adsorbed from benzene (50 c.c.) on alumina (80 g.). Elution with benzene–ether (3 : 1; 800 c.c.) gave ester B as needles, m. p. 147—151°. The aqueous solution was acidified with concentrated hydrochloric acid and kept at 20° for 1 hr. Ethereal extraction did not afford a ketonic fraction.

Attempted Reduction of Ester B with Sodium Borohydride.—Ester B (450 m.g.) in pure dioxan (30 c.c.) was treated with sodium borohydride (85 m.g.) in aqueous dioxan (1 : 1; 30 c.c.) at 20° for 1 hr. Dilution with water and isolation with ether gave a product which was adsorbed from benzene (30 c.c.) on alumina (45 g.). Elution with benzene–ether (9 : 1; 900 c.c.) yielded starting material, m. p. 147—148° (from methanol or acetone).

Oxidation of Ester B.—Ester B (130 mg.) in acetone (25 c.c.) was oxidised with chromic acid in the usual manner.[8] Isolation with ether gave a gum which was adsorbed from light petroleum (20 c.c.) on alumina (10 g.). Elution with light petroleum–benzene (1 : 1; 500 c.c.) yielded a gum (90 mg.) which crystallised from dilute methanol or dilute alcohol as needles, m. p. 158—159°, $[\alpha]_D$ +88·5° (*c* 1·09) (Found: C, 73·4; H, 8·85. $C_{33}H_{48}O_6$ requires C, 73·3; H, 8·95. Calc. for $C_{32}H_{46}O_6$: C, 72·95; H, 8·8%). This *compound* had $\lambda_{max.}$ (broad) at 2130 Å (ε 18,000) and $\nu_{max.}$ 1735 and 1708 (very broad and intense band with two maxima), 1650, 860, and 820 cm.$^{-1}$.

Examination of Fraction 2 *from the Alcohol Extract.*—This fraction (1·3 g.) was adsorbed from benzene (120 c.c.) on alumina (100 g.) and eluted as follows: benzene–ether (9 : 1; 300 c.c.), solid (170 mg.), m. p. 143—146° (fraction 1); benzene–ether (1 : 1; 700 c.c.), sticky solid (550 mg.) (fraction 2); ether (400 c.c.), yellow gum (380 mg.) (fraction 3).

Fraction 1 crystallised from methanol, to give ester B as needles, m. p. 146—149°.

Fraction 2 was adsorbed from benzene (20 c.c.) on alumina (35 g.). Elution with benzene–ether (1 : 1; 300 c.c.) yielded a small amount of crystalline material, m. p. 190—193° (mainly ester C).

[8] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2555.

XUM

Fraction 3 did not crystallise.

Comparison of constants.

Name of compound	M. p.	$[\alpha]_D$	Constants of the corresponding trametenolic acid derivative: M. p.	$[\alpha]_D$
3β-Hydroxylanosta-8 : 24-dien-21-oic acid...	253—258°	+43° *	259—261°	+47° †
3β-Acetoxylanosta-8 : 24-dien-21-oic acid ...	240—244	+48 *	209—211	—
Me 3β-hydroxylanosta-8 : 24-dien-21-oate ...	132—135	+52	127—128	+59
Me 3β-acetoxylanosta-8 : 24-dien-21-oate ...	147—149	+63	104—106	—
Me 3-oxolanosta-8 : 24-dien-21-oate [a]	121—123	+69	105—107	—
3-Oxolanosta-8 : 24-dien-21-oic acid [a]	197—202	+68	204—206	—
Lanosta-8 : 24-diene-3β : 21-diol [b]	189—192	+57 *	199—200	—
Lanosta-8 : 24-diene [c]	79·5—80	+65	85—87	+66

* In pyridine. † In methanol.
[a] Ref. 4. [b] Halsall and Sayer, preceding paper. [c] McGhie, Pradhan, and Cavalla, *J.*, 1952, 3176.

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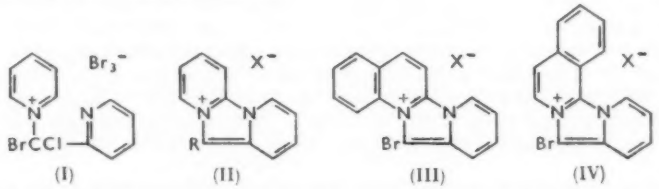
410. *Polynuclear Heterocyclic Systems. Part III.*[1] *The Synthesis of Dipyridinoglyoxalinium and Related Salts.*

By B. R. BROWN and J. HUMPHREYS.

Dipyridino(1′ : 2′-1 : 2, 1″ : 2″-3 : 4)-, 5-bromodipyridino(1′ : 2′-1 : 2, 1″ : 2″-3 : 4)-, 5-bromodipyridino(1″ : 2″-3 : 4)quinolino(1′ : 2′-1 : 2)-, and 5-bromopyridino(1″ : 2″-3 : 4)*iso*quinolino(2′ : 1′-1 : 2)-glyoxalinium salts have been prepared from ω-bromo-α-picoline.

IT has not been possible, by using the methods previously described,[1,2] to obtain glyoxalinium salts from ωω-dichloro-α-picoline.[3] This compound formed a quaternary salt, not a glyoxalinium salt, with pyridine. Bromination of the quaternary salt gave the bromo-quaternary salt (I) without cyclisation.

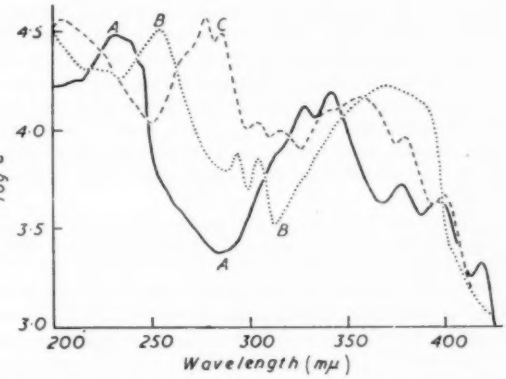


(I) (II) (III) (IV)

It is not possible to brominate α-picoline directly.[4] It is unchanged after treatment with bromine at 90° for several days in acetic acid containing sodium acetate; the acetic acid is preferentially brominated and bromoform can be isolated. Attempts to brominate picoline 1-oxide and ω-bromo-α-picoline were unsuccessful.

[1] Part II, Brown and White, *J.*, 1957, 1589.
[2] Brown and Wild, *J.*, 1956, 1158.
[3] Dyson and Hammick, *J.*, 1939, 781.
[4] Brown, Hammick, and Thewlis, *J.*, 1951, 1145.

ω-Bromo-α-picoline [5] has been obtained in quantity by conversion of α-picoline 1-oxide into 2-hydroxymethylpyridine [6] and direct reaction of this with aqueous hydrobromic acid. Reaction of the crude ω-bromo-α-picoline with pyridine, quinoline, and *iso*quinoline yielded the quaternary bromides which were characterised as dipicrates. Bromination of these bromides and spontaneous ring closure yielded the corresponding glyoxalinium salts (II, R = Br; III; and IV), the characteristic absorption spectra of which are illustrated.



Ultraviolet spectra in ethanol: (*A*) 5-*Bromodipyridino*(1′ : 2′-1 : 2, 1″ : 2″-3 : 4)*glyoxalinium bromide* (II; R = Br); (*B*) 5-*bromopyridino*(1″ : 2″-3 : 4)*quinolino*(1′ : 2′-1 : 2)*glyoxalinium bromide* (III); and (*C*) 5-*bromopyridino*(1″ : 2″- 3 : 4)*iso*quinolino(2′ : 1′-1 : 2)*glyoxalinium bromide* (IV).

Dipyridino(1′ : 2′-1 : 2, 1″ : 2″-3 : 4)glyoxalinium salts (II; R = H) have been prepared from ω-bromo-α-picoline and 2-bromopyridine. This method is less efficient than the others available for glyoxalinium salts [2] but, as ωω-dibromo-α-picoline is not available, it is the most convenient way to obtain the parent compound of the series.

Experimental

1-(α-*Chloro*-α-2-*pyridylmethyl*)*pyridinium Chloride*.—A solution of ωω-dichloro-α-picoline [3] (Found: C, 44·8; H, 3·3. Calc. for $C_6H_5NCl_2$: C, 44·5; H, 3·1%) (5·0 g.) in pyridine (30 ml.) was boiled under reflux for 2 hr. Decantation of pyridine left hygroscopic crystals (1·5 g.) which were crystallised several times from methanol–ether to give the *chloride hemihydrate* as colourless needles (Found: C, 52·75; H, 4·7; N, 11·1; Cl, 28·5. $C_{11}H_{10}N_2Cl_2,\frac{1}{2}H_2O$ requires C, 52·8; H, 4·4; N, 11·2; Cl, 28·4%). The ultraviolet spectrum in ethanol showed the compound to be a simple pyridine derivative.

1-(α-*Bromo*-α-*chloro*-α-2-*pyridylmethyl*)*pyridinium Perbromide*.—A mixture of the above pyridinium chloride (0·5 g.), glacial acetic acid (10 ml.), fused sodium acetate (0·5 g.), and bromine (0·8 ml.) was boiled under reflux for 2 hr. The precipitate (0·3 g.) crystallised from acetic acid as brown needles of the *perbromide* (Found: C, 25·5; H, 1·3; Hal, 69·3. $C_{11}H_9N_2ClBr_4$ requires C, 25·2; H, 1·7; Hal, 67·8%).

ω-*Bromo*-α-*picoline*.[5]—To ice-cold acetic anhydride (250 ml.) was added 48% hydrobromic acid (63 ml.) and 2-hydroxymethylpyridine acetate [6] (7·7 g.), and the mixture was heated at 100° for 4 hr. Evaporation under reduced pressure gave the crude ω-bromo-α-picoline hydrobromide which was dissolved in water and treated with aqueous sodium hydroxide; the liberated ω-bromo-α-picoline was taken up in benzene and dried. No attempt was made to purify the ω-bromopicoline as it is known to be unstable.[5] Evaporation of the benzene solution left a yellow lachrymatory oil.

Dipyridino(1′ : 2′-1 : 2, 1″ : 2″-3 : 4)*glyoxalinium Salts* (II; R = H).—A solution of ω-bromopicoline (4·0 g.) and 2-bromopyridine (4·0 g.) in benzene (70 ml.) was boiled under reflux for 4 days. The deposit of brown crystals was washed several times with benzene, dissolved in water (30 ml.), boiled with charcoal, and filtered off. The filtrate was made just alkaline with aqueous sodium hydroxide at 0° and extracted several times with ether to remove unchanged starting materials.

[5] Cf. Šorm and Šedivý, *Coll. Czech. Chem. Comm.*, 1948, **13**, 289.
[6] Boekelheide and Linn, *J. Amer. Chem. Soc.*, 1954, **76**, 1286.

XUM

Half of the resulting aqueous solution was treated with excess of 60% perchloric acid, and the precipitated *perchlorate* was separated, washed with water, and crystallised several times from methanol to afford pale brown plates (0·80 g.) (Found: C, 49·5; H, 3·3; N, 10·85; Cl, 13·9. $C_{11}H_{19}O_4N_2Cl$ requires C, 49·2; H, 3·35; N, 10·4; Cl, 13·2%), $\lambda_{max.}$ in ethanol 227, 236, 272, 284, 319, 334, 364, 381, and 402 mμ (log ε 4·52, 4·49, 3·37, 3·32, 4·09, 4·18, 3·68, 3·60, and 3·31), $\lambda_{min.}$ 234, 267, 279, 286, 325, 355, 374, and 395 mμ (log ε 4·46, 3·36, 3·28, 3·31, 3·99, 3·57, 3·46, and 3·13).

The other half of the solution was acidified with aqueous hydrobromic acid and treated with excess of hot aqueous picric acid. The precipitated *picrate* was crystallised several times from acetic acid to give yellow needles (0·70 g.), m. p. 200—210° (decomp.) (Found: C, 51·65; H, 2·8; N, 17·7. $C_{17}H_{11}O_7N_5$ requires C, 51·4; H, 2·8; N, 17·6%).

1-(2-*Pyridylmethyl*)*pyridinium Bromide*.—Pyridine (10 ml.) was added to a solution of ω-bromopicoline (4·0 g.) in benzene (50 ml.) and the mixture was boiled for 15 min. Next day the benzene was decanted and the solid crystallised from ethanol–ether to yield colourless, hygroscopic needles (2·0 g.). The derived *dipicrate* separated from aqueous methanol as orange plates, m. p. 158° (Found: C, 44·0; H, 2·6; N, 17·8. $C_{23}H_{16}O_{14}N_8$ requires C, 43·95; H, 2·55; N, 17·8%).

The same dipicrate, m. p. and mixed m. p. 158° (Found: C, 44·0; H, 2·7; N, 17·5%), was obtained by treating the product from ω-monochloro-α-picoline and pyridine with picric acid.

5-*Bromodipyridino*(1′ : 2′-1 : 2, 1″ : 2″-3 : 4)*glyoxalinium Salts* (II; R = Br).—Bromination of 1-(2-pyridylmethyl)pyridinium bromide (1·5 g.) as described previously for similar quaternary salts [1] yielded the *glyoxalinum perbromide* (2·4 g.) as orange needles from acetic acid (Found: C, 27·0; H, 1·7; N, 5·5; Br, 65·7. $C_{11}H_8N_2Br_4$ requires C, 27·1; H, 1·65; N, 5·7; Br, 65·5%). Treatment of the perbromide (1·3 g.) with pyridine gave the *bromodipyridinoglyoxalinium bromide* (0·8 g.) which separated from methanol as pale yellow needles (Found: C, 40·0; H, 2·4; N, 8·7; Br, 48·9. $C_{11}H_8N_2Br_2$ requires C, 40·2; H, 2·5; N, 8·5; Br, 48·8%). The *picrate* separated from acetone as slender yellow needles, m. p. 208° (Found: C, 43·1; H, 2·1. $C_{17}H_{10}O_7N_5Br$ requires C, 42·95; H, 2·1%).

1-(2-*Pyridylmethyl*)*quinolinium Bromide*.—ω-Bromopicoline (3 g.) and quinoline (7 ml.) in boiling benzene (25 ml.) gave an oily quaternary salt. The derived *dipicrate* separated from ethanol as orange needles, m. p. 173° (Found: C, 48·1; H, 2·6; N, 16·4. $C_{27}H_{18}O_{14}N_8$ requires C, 47·8; H, 2·65; N, 16·5%).

5-*Bromopyridino*(1″ : 2″-3 : 4)*quinolino*(1′ : 2′-1 : 2)*glyoxalinium Salts* (III).—Bromination of the crude pyridylmethylquinolinium bromide (2·2 g.) and treatment with pyridine yielded the *pyridinoquinolinoglyoxalinium bromide hydrate* (1·1 g.) which separated from methanol–ether as yellow needles (Found: C, 45·7; H, 3·2; N, 7·2; Br, 40·0. $C_{15}H_{10}N_2Br_2,H_2O$ requires C, 45·5; H, 3·0; N, 7·1; Br, 40·4%). The infrared spectrum in Nujol contains a band at 3450 cm.$^{-1}$. The derived *perchlorate* separated from methanol as pale brown needles (Found: C, 45·4; H, 2·6; N, 7·35. $C_{15}H_{10}O_4N_2ClBr$ requires C, 45·3; H, 2·5; N, 7·1%). The *picrate* separated from acetone as yellow needles, m. p. 231° (Found: C, 48·0; H, 2·4. $C_{21}H_{12}O_7N_5Br$ requires C, 48·0; H, 2·3%).

2-(2-*Pyridylmethyl*)iso*quinolinium Bromide*.—*iso*Quinoline (5·0 g.) and ω-bromopicoline (2 g.) in boiling benzene (25 ml.) gave a red solid quaternary bromide (2·5 g.). The derived *dipicrate* separated from methanol–acetone as yellow plates, m. p. 188° (Found: C, 48·2; H, 2·7; N, 16·9. $C_{27}H_{18}O_{14}N_8$ requires C, 47·8; H, 2·65; N, 16·5%).

5-*Bromopyridino*(1″ : 2″-3 : 4)iso*quinolino*(2′ : 1′-1 : 2)*glyoxalinium Salts* (IV).—The above crude quaternary salt (2·1 g.) was brominated, and the product treated with pyridine to yield the *glyoxalinium bromide monohydrate* (1·6 g.) which separated from methanol–ether as pale brown needles (Found: C, 45·2; H, 2·8; Br, 40·3. $C_{15}H_{10}N_2Br_2,H_2O$ requires C, 45·5; H, 3·0; Br, 40·4%). The infrared spectrum in Nujol contains a band at 3450 cm.$^{-1}$. The derived *perchlorate* separated from methanol as colourless needles (Found: C, 45·5; H, 2·7; N, 6·7. $C_{15}H_{10}O_4N_2ClBr$ requires C, 45·3; H, 2·5; N, 7·1%).

We thank Mr. D. S. Taylor for help with the preparation of dipyridinoglyoxalinium perchlorate.

Dyson Perrins Laboratory, Oxford University. [*Received, January* 13*th*, 1959.]

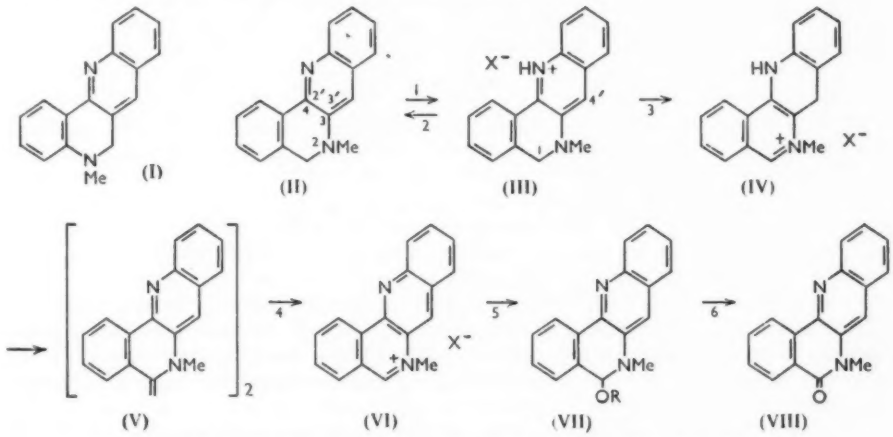
411. *The Structure and Properties of Certain Polycyclic Indolo- and Quinolino-derivatives. Part XII.*[1] 1 : 2-*Dihydro-2-methylquinolino*(3′ : 2′-3 : 4)iso*quinoline and its Derivatives.*

By I. G. Hinton and Frederick G. Mann.

1 : 2-Dihydro-2-methylquinolino(3′ : 2′-3 : 4)*iso*quinoline has been prepared by the condensation of 1 : 2 : 3 : 4-tetrahydro-2-methyl-4-oxo*iso*quinoline and *o*-aminobenzaldehyde. The properties of this base, and particularly the isomerisation of its salts and the products obtained from these salts, have been studied: the base undergoes atmospheric oxidation, both in the solid state and readily in solution, to the corresponding cyclic amide.

The properties of this base, and those of the isomeric 1 : 2-dihydro-1-methylquinolino(3′ : 2′-3 : 4)quinoline studied earlier, show some similarities and also some marked differences.

The properties of the yellow 1 : 2-dihydro-1-methylquinolino(3′ : 2′-3 : 4)quinoline (I), particularly the formation of its purple monohydrochloride, the conversion of the latter by hot acid into the yellow monohydrochloride of the isomeric 1 : 4′-dihydro-base, the thermal conversion of this isomer into the original base (I), and the ready atmospheric oxidation of both isomers to the cream-coloured 1 : 2-dihydro-1-methyl-2-oxoquinolino-(3′ : 2′-3 : 4)quinoline, have been extensively studied.[2]



Our recent synthesis of 1 : 2 : 3 : 4-tetrahydro-2-methyl-4-oxo*iso*quinoline [3] has now enabled us to condense this keto-amine with *o*-aminobenzaldehyde to form the yellow 1 : 2-dihydro-2-methylquinolino(3′ : 2′-3 : 4)*iso*quinoline (II), which is isomeric with the base (I), and to study its reactions under comparable conditions.

The structure of the yellow base (II), m. p. 92—93°, is shown by its synthesis, by its analysis and molecular weight, and by its infrared spectrum which shows a sharp moderately strong band at 2780 cm.$^{-1}$ (indicating an =NMe group [4]) but gives no indication of an =NH group. It sublimes without decomposition at 82°/0·002 mm., but undergoes

[1] Part XI, Braunholtz and Mann, *J.*, 1958, 3377.
[2] *Idem*, *J.*, 1955, 381; 1958, 3368.
[3] I. G. Hinton and Mann, *J.*, 1959, 599.
[4] Braunholtz, Ebsworth, Mann, and Sheppard, *J.*, 1958, 2780.

atmospheric oxidation readily in cold ethanolic solution and also in the solid state (see p. 2045): consequently its preparation and recrystallisation should be conducted under nitrogen. It acts apparently as a monoacidic base, for the addition of hydrochloric or hydrobromic acid to its cold acetone solution precipitated the red mono-hydrochloride and -hydrobromide, which when treated with aqueous sodium hydroxide regenerated the base (II). These salts have the structure (III), for the infrared spectrum of the hydrochloride has a broad band centred at 2610 cm.$^{-1}$ indicating the $\equiv NH^+$ group, and a band of moderate strength at 2780 cm.$^{-1}$ indicating the =NMe group.

When the hydrochloride (III; X = Cl) in concentrated hydrochloric acid was boiled, isomerisation to the golden-yellow quaternary chloride (IV; X = Cl) occurred. The infrared spectrum of the corresponding quaternary perchlorate showed a sharp band at 3350 cm.$^{-1}$ indicating an =NH group, but gave no evidence of an =NMe or $\equiv NH^+$ group.

Adding an excess of aqueous sodium hydroxide to an aqueous solution of the chloride (IV; X = Cl) gave a purple precipitate which, however, became yellow when the mixture

FIG. 1. *Ultraviolet spectra of the base* (V) (*A*) *in ethanol and* (*B*) *in ethanol containing* 1 *drop of concentrated hydrochloric acid, and* (*C*) *of the perchlorate* (VI; X = ClO_4) *in ethanol.*

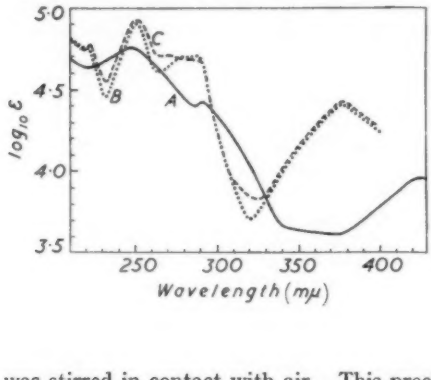
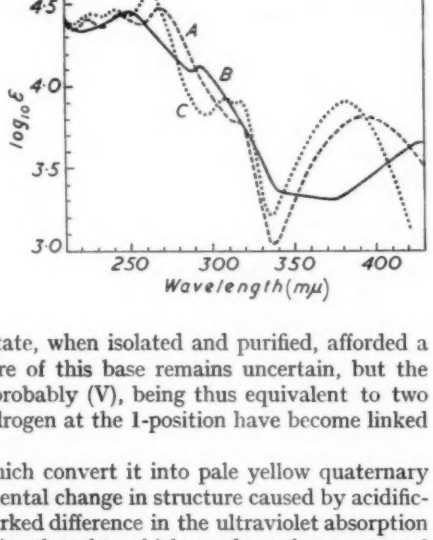


FIG. 2. *Ultraviolet spectra of* (*A*) *the base* (II), (*B*) *the base* (V), *and* (*C*) *the base* (VII; R = Et). *For strict comparison with* (*A*) *and* (*C*), *the curve* (*B*) *is plotted for values of* $\log_{10} \varepsilon/2$, *since the intensities are approximately the sum of those of the two halves of the molecule acting independently.*



was stirred in contact with air. This precipitate, when isolated and purified, afforded a bright yellow base, m. p. 214°. The structure of this base remains uncertain, but the evidence discussed below indicates that it is probably (V), being thus equivalent to two molecules of the base (II) which by loss of hydrogen at the 1-position have become linked by a double bond.

The base (V) is very sensitive to acids, which convert it into pale yellow quaternary salts of structure (VI). The rapid and fundamental change in structure caused by acidification of the base (V) is shown (Fig. 1) by the marked difference in the ultraviolet absorption spectra of the base (*A*) in ethanol alone and (*B*) in ethanol to which one drop of concentrated hydrochloric acid has been added. The spectrum in the acidified solution is almost identical with that (*C*) of the pure crystalline perchlorate (VI; X = ClO_4) obtained similarly by acidification of the base (V). The structure of the perchlorate is confirmed by its infrared spectrum, which shows the absence of =NH, =NMe, and $\equiv NH^+$ groups, and by its ultraviolet spectrum (Fig. 1), which shows the intense absorption in the 250—260 mμ region which is typical of many extended polycyclic aromatic systems.

A suspension of the perchlorate (VI; X = ClO_4) in aqueous sodium hydroxide, when treated with hot ethanol to give complete dissolution, deposited on cooling the yellow 1-ethoxy-base (VII; R = Et), m. p. 159—160°, which was stable in boiling ethanolic solution, from which it could be recrystallised: the addition of perchloric acid to this

solution, however, rapidly regenerated the perchlorate (VI; X = ClO_4). The structure of the base is shown by the infrared spectrum, which gives no evidence for an –OH or =CO group, and the oxygen must therefore be present in a C–O–C unit: the =NMe group appears as a weak band at 2805 cm.$^{-1}$, but as a stronger and sharper band at 2820 cm.$^{-1}$ in the homologue (VII; R = Me). The ultraviolet spectrum of the base (VII; R = Et) is closely similar to that of the base (II) (Fig. 2).

The base (VII; R = Et) is of course the *O*-ethyl derivative of the ψ-base corresponding to the quaternary base (VI; X = OH). This ready reaction of the ψ-base with alcohols to form an ether and with acids to re-form the normal salts represents the usual behaviour of such bases.

A cold ethanolic solution of the initial base (II), when allowed to evaporate spontaneously, underwent oxidation to the colourless 1-oxo-compound (VIII). Fine crystals of the base (II) on exposure to air also underwent this rapid oxidation. The bases (V) and (VII) gave indication of this atmospheric oxidation very much more slowly, but were rapidly oxidised to the compound (VIII) by a warm acetone solution of potassium permanganate. The infrared spectrum of the compound (VIII) shows a band at 1642 cm.$^{-1}$ typical of the amide-carbonyl group; the normal band characteristic of the =NMe group is of course not produced by the CO·NMe unit.[4] The compound (VIII) is weakly basic, and its salts dissociated on attempted recrystallisation. This ready oxidation of the base (II) is thus strictly analogous to that of the base (I), which gives the isomeric 2-oxo-derivative.

The evidence which indicates the structure (V) for the yellow base, m. p. 214°, may now be summarised. (*a*) Analysis and molecular weight determinations: the low solubility in boiling solvents and the small elevation of b. p. precluded accurate determinations but the values for the molecular weight uniformly approached that required for formula (V). (*b*) The ready oxidation of the bases (II), (V), and (VII; R = Me or Et) to the 1-oxo-derivative (VIII) indicate that these bases can differ only at the 1-position, where the atoms or groups attached must, therefore, be reasonably susceptible to replacement by oxygen. (*c*) The infrared spectra of the above bases are very closely similar, except that the spectrum of the base (V) does not show the band characteristic of the =NMe group. This is not surprising, for the band is shown only when the lone pair of electrons on the nitrogen atom is unaffected by neighbouring groups,[4] and the long conjugated chain in the structure (V) might induce some electronic drift from the nitrogen atoms in the =NMe groups. Alternatively, the steric crowding about the central double bond may force the two halves out of coplanarity, which might also affect the nitrogen atom. (*d*) The ultraviolet spectrum of the base (V) has a general similarity to those of the bases (II) and (VII; R = Et), more particularly in the 210—340 mμ region (Fig. 2). (*e*) Each half of the molecule (V) can be regarded systematically as the major portion of an anhydro-base, and the action of acids in splitting this dual system so readily into two molecules of the corresponding salt (VI) would therefore be expected.

The initial purple material produced by the addition of sodium hydroxide to the chloride (IV; X = Cl) was not investigated because of its rapid aerial oxidation. The formation of a base of structure (V) under these circumstances must be a complex process, but quaternary *iso*quinolinium salts are known to give many complex reactions in the presence of alkali and air.[5]

The action of methyl iodide on the above bases may be briefly noted. The base (II) when boiled with an excess of methyl iodide gave pale yellow needles of composition $C_{19}H_{19}ON_2I$ or $C_{19}H_{21}ON_2I$, the structure of which has not been elucidated. The mother-liquor yielded small quantities of the base (VII; R = Me) and also of the 1-oxo-compound (VIII), undoubtedly formed by direct oxidation of the base (II). The base (V) was recovered in high yield after its solution in methyl iodide had been boiled for 6 hours, the

[5] Cf. Gensler, "Heterocyclic Compounds," ed. by Elderfield, Wiley, New York, 1952, Vol. IV, p. 469.

low reactivity of the =NMe groups being caused probably by steric hindrance. When the base in methyl iodide was heated at 100° for 7 hours, it deposited a crude iodide which furnished a pure yellow perchlorate of composition $C_{19}H_{17-19}O_5N_2Cl$, which has not been identified. The base (VII; R = Me) when boiled in methanolic methyl iodide yielded the iodide (VI; X = I) and the oxo-compound (VIII).

The comparative properties of the isomeric bases (I) and (II) can now be summarised. The conversion of the base (II) by cold hydrochloric acid into the hydrochloride (III; X = Cl) is identical in type with that shown by the base (I). The action of hot hydrochloric acid on the salt (III; X = Cl) is to cause migration of a hydrogen atom to the 4′-position, as in the previous series, but this atom now has to come from the 1-position, with consequent aromatisation of the pyridine ring and the formation of a quaternary chloride, in contrast to the tertiary amine hydrochloride in the earlier series. The base (II), being structurally unable to undergo a strict allylic transformation, cannot exist in an isomeric form, and in this respect differs markedly from the base (I). The stages represented by the compounds (V), (VI), and (VII), being determined specifically by the *iso*quinoline ring, have no parallel in derivatives of the base (I). The close analogy returns, however, at the final oxidation stage (VIII), which is again identical in type with the isomeric oxidation product of the base (I).

One further significant difference arises. The yellow colour of the base (I) and the deep red colour of its salts (corresponding in type to III) can be readily explained by the nature of the canonical contributions of the resonance hybrid of these compounds.[2] A similar explanation of colour cannot be applied to the yellow base (II) and its red salts (III), owing to the " blocking " effect of the methylene group between the =NMe group and the *o*-phenylene ring. Moreover in the case of the salts, it must be borne in mind that the production of marked colour by the addition of one proton to a diamine, owing to the resonance of the cation thus formed, is almost invariably dependent on the nitrogen atoms' being joined by an odd number of carbon (or other) atoms. This requirement is met in the base (I) but is absent in the isomeric base (II). It is clear that the base (II) can be added to the other diamines of comparable structure recently discussed by Murrell,[6] all of which form salts whose marked colour cannot be explained by classical or resonance theories, but for which Murrell has suggested an explanation based on molecular-orbital considerations.

An attempt to prepare the 4′-carboxylic acid of the base (II), by the Pfitzinger reaction (involving isatin in hot alkaline solution) from tetrahydro-2-methyl-4-oxo*iso*quinoline, was unsuccessful. No decisive product was isolated after prolonged heating of the reaction mixture under nitrogen, and the reactants were recovered after milder conditions had been employed.

Experimental

Consistent m. p.s of certain compounds were obtained only by the use of evacuated capillary tubes, noted as (E.T.), the immersion temperature if above room temperature being denoted (I.T.).

o-Aminobenzaldehyde was prepared by Mann and Wilkinson's modification [7] of Smith and Opie's method.[8]

1 : 2-*Dihydro*-2-*methylquinolino*(3′ : 2′-3 : 4)iso*quinoline* (II).—A solution of *o*-aminobenzaldehyde (4·5 g.) in ethanol (40 c.c.) was treated in turn with tetrahydro-2-methyl-4-oxo*iso*quinoline hydrochloride (7 g., 1 mol.) and 10% aqueous sodium hydroxide (32 c.c., 4 mols.), and the solution was set aside under nitrogen overnight. After *ca.* 7 hr. a dark yellow oil separated and later crystallised. The crystals, when both collected and recrystallised from ethanol under nitrogen, gave the iso*quinoline* (II), yellow needles, m. p. 92—93° (E.T.) (Found: C, 83·3; H, 6·0%; *M*, ebullioscopic in 0·702% acetone solution, 220; in 0·656% ethanolic solution, 230. $C_{17}H_{14}N_2$ requires C, 82·9; H, 5·7%; *M*, 246).

[6] Murrell, *J.*, 1959, 296.
[7] Mann and Wilkinson, *J.*, 1957, 3346.
[8] Smith and Opie, *Org. Synth.*, 1948, **28**, 11.

The addition of dilute hydrochloric acid to an acetone solution of the base deposited the bright red *hydrochloride* (III; X = Cl), m. p. 278° (I.T., 270°) without recrystallisation (Found: C, 71·1; H, 5·4; N, 9·5. $C_{17}H_{14}N_2$,HCl requires C, 72·2; H, 5·3; N, 9·9%). The *hydrobromide* (III; X = Br), prepared by adding 45% hydrobromic acid to the ethanolic base, formed dull red crystals (Found: C, 62·3; H, 4·8; N, 8·6. $C_{17}H_{14}N_2$,HBr requires C, 62·4; H, 4·6; N, 8·6%). The red insoluble *chloroplatinate*, when collected, washed with ethanol, and dried, charred gradually from 120° (Found: C, 45·1; H, 3·4; Pt, 21·3. $2C_{17}H_{14}N_2,H_2PtCl_6$ requires C, 45·2; H, 3·4; Pt, 21·6%).

Picric acid, when added to the base (II), each in ethanolic solution, precipitated a bright red picrate which when recrystallised from ethanol containing a small quantity of picric acid, gave a mixture of yellow and red crystals, m. p. 175—185°, which could not be satisfactorily separated and identified.

A cold aqueous solution of the hydrochloride (III; X = Cl), when treated with aqueous sodium hydroxide, deposited the base (II).

1′ : 4′-Dihydro-2-methylquinolino(3′ : 2′-3 : 4)iso*quinolinium Chloride* (IV; X = Cl).—A suspension of the base (II) (2·5 g.) in concentrated hydrochloric acid (100 c.c.) was boiled under reflux until the clear red solution, which had become paler, suddenly deposited a thick suspension of orange crystals. The mixture was set aside for 48 hr., and the *chloride* (IV; X = Cl), when collected from the yellow solution and recrystallised from 50% aqueous ethanol, formed golden-yellow crystals, m. p. 288° (Found: C, 72·1; H, 5·3; N, 9·8. $C_{17}H_{15}N_2Cl$ requires C, 72·2; H, 5·3; N, 9·9%). The perchlorate (IV; X = ClO_4), obtained by the addition of 60% perchloric acid to the hot ethanolic solution of the chloride, and recrystallised from aqueous ethanol, had m. p. 270° (I.T. 260°).

Bi-[*1 : 2-dihydro-2-methylquinolino*(3′ : 2′-3 : 4)iso*quinol-1-ylidene*] (V).—A large excess of 10% aqueous sodium hydroxide was added to a stirred aqueous solution of the chloride (IV; X = Cl). The purple precipitate became yellow when it was near the surface of the solution, and the mixed product was then twice extracted with ether. The deep-maroon ethereal extract was washed with water and diluted with ethanol, charcoal added, and the ether removed. The residual ethanolic solution, when boiled and filtered, was deep yellow and on cooling deposited bright yellow plates of the *base* (V), m. p. 214° (E.T., I.T., 100°) after crystallisation from ethanol (Found: C, 82·4; H, 5·9; N, 11·2%; *M*, in boiling 0·471% acetone solution, 430; in 0·636% solution, 420; in 0·648% ethyl methyl ketone solution, 400. $C_{34}H_{24}N_4$ requires C, 83·5; H, 5·0; N, 11·5%; *M*, 488. Low carbon but satisfactory hydrogen values were obtained by using normal combustion temperatures: higher temperatures gave rather better carbon values but, as usual, increased the hydrogen values).

2-Methylquinolino(3′ : 2′-3 : 4)iso*quinolinium Perchlorate* (VI; X = ClO_4).—A warm ethanolic solution of the base (V), when treated dropwise with 60% aqueous perchloric acid and then cooled, deposited the crude red *perchlorate* (VI; X = ClO_4) which after recrystallisation from 50% aqueous ethanol formed pale yellow needles, m. p. 310—312° (E.T.) (Found: C, 58·6; H, 4·0; N, 8·0. $C_{17}H_{13}O_4N_2Cl$ requires C, 59·2; H, 3·8; N, 8·1%). The similar use of dilute sulphuric acid gave the *hydrogen sulphate* (VI; X = HSO_4), pale yellow crystals, m. p. 307—309° (effervescence) (E.T., I.T. 300°) (from aqueous ethanol) (Found: C, 59·3; H, 4·4; N, 8·1. $C_{17}H_{14}O_4N_2S$ requires C, 59·6; H, 4·1; N, 8·2%). The addition of dilute hydrochloric acid to an acetone solution of the base (V) deposited the crude chloride (VI; X = Cl), for which no suitable solvent for crystallisation was found. All these salts had a marked sternutatory action.

1-Ethoxy-1 : 2-dihydro-2-methylquinolino(3′ : 2′-3 : 4)iso*quinoline* (VII; R = Et).—A suspension of the perchlorate (VI; X = ClO_4) in warm 10% aqueous sodium hydroxide was diluted with sufficient hot ethanol to give a clear solution, which was then cooled and extracted with ether. The ethereal extract was diluted with ethanol, charcoal added, and the ether removed. The residual solution, when boiled under nitrogen, filtered and cooled, deposited the *1-ethoxy-compound* (VII; R = Et), bright yellow crystals, m. p. 159—160° (E.T.) after four recrystallisations from ethanol under nitrogen and drying at 40°/0·1 mm. in nitrogen (Found: C, 78·6; H, 6·3; N, 9·5%; *M*, in boiling 0·732% ethanolic solution, 300. $C_{19}H_{18}ON_2$ requires C, 78·6; H, 6·2; N, 9·6%; *M*, 290). An ethanolic solution of this base, when treated with perchloric acid, deposited the perchlorate (VI; X = ClO_4), m. p. and mixed m. p. 310° (E.T.).

Oxidation to 1 : 2-*Dihydro-2-methyl-1-oxoquinolino*(3′ : 2′-3 : 4)iso*quinoline* (VIII).—(*A*) An ethanolic solution of the base (II) was allowed to evaporate to dryness on a clock-glass at room temperature during 24 hr. The brownish-yellow residue, when recrystallised from ethanol,

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sublimed at *ca.* 200°/0·1 mm., and again recrystallised, afforded the 1-*oxo-derivative* (VIII), colourless plates, m. p. 219—220° (Found: C, 78·2; H, 4·5; N, 11·0. $C_{17}H_{12}ON_2$ requires C, 78·4; H, 4·6; N, 10·8%). The pure powdered crystalline base (II) on exposure to air becomes dull yellowish-brown in *ca.* 2 hr. as this oxidation proceeds.

(*B*) Potassium permanganate was added to the base (V), each in warm acetone solution, until decolorisation of the former ceased. The solvent was evaporated and the residue extracted with ether. Removal of the ether left a residue of the compound (VIII), m. p. and mixed m. p. 217—220° after purification as before.

(*C*) A similar result was obtained when the base (VII; R = Et) was thus oxidised.

The onset of atmospheric oxidation of the crystalline bases (V) and (VII; R = Et) at room temperature is revealed only by their colours, which very slowly become duller and darker.

An ethereal solution of the base (VIII) when treated with hydrogen chloride deposited the hydrochloride: an ethanolic solution of the base, with perchloric acid, deposited the perchlorate. Both these yellow salts dissociated on attempted recrystallisation.

Action of Methyl Iodide.—(A) *The base* (II). A solution of this base in an excess of methyl iodide was boiled under reflux in nitrogen for 4 hr., pale yellow crystals separating from the orange solution. The crystals, when collected from the cold mixture and recrystallised from methanol, formed very pale yellow needles, m. p. 140—141° (effervescence) (E.T., I.T. 115°) (Found: C, 54·8; H, 4·8; N, 7·0. $C_{19}H_{19}ON_2I$ requires C, 54·6; H, 4·6; N, 6·7. $C_{19}H_{21}ON_2I$ requires C, 54·3; H, 5·0; N, 6·7%). The infrared spectrum showed a band caused by an –OH or =NH group. A methanolic solution of this compound with perchloric acid gave an almost colourless *perchlorate*, m. p. 230—233° (E.T., I.T. 220°) (Found: C, 58·7; H, 5·1; N, 7·3. $C_{19}H_{19}O_5N_2Cl$ requires C, 58·4; H, 4·9; N, 7·2. $C_{19}H_{17}O_5N_2Cl$ requires C, 58·7; H, 4·4; N, 7·2%).

The methyl iodide mother-liquor was treated with much ether to precipitate more crude methiodide, and was then filtered and diluted with a small volume of methanol, and the ether was removed. The methanolic solution, when boiled (charcoal), filtered, and cooled, deposited a yellow oil which solidified. Fractional crystallisation of the solid gave (*a*) the 1-oxo-compound (VIII), colourless plates, m. p. 220° (E.T., I.T. 115°), mixed m. p. 222—223° (E.T., I.T. 205°), and (*b*) the 1-*methoxy-compound* (VII; R = Me), yellow crystals, m. p. 111—112° (E.T., I.T. 90°) (Found: C, 78·2; H, 5·8; N, 10·1. $C_{18}H_{16}ON_2$ requires C, 78·2; H, 5·8; N, 10·1%). A methanolic solution of this compound treated with perchloric acid gave the perchlorate (VI; X = ClO_4). The identity of the 1-methoxy-base (VII; R = Me) was confirmed by its preparation as yellow crystals, m. p. 111—113°, by the addition of 10% aqueous sodium hydroxide to a methanolic solution of the perchlorate (VI; X = ClO_4).

(B) *The base* (V). The base in methyl iodide solution, when boiled under reflux in nitrogen for 6 hr., deposited a trace of a reddish solid, but was otherwise unaffected. When the original solution was heated in a sealed tube under nitrogen at 100° for 7 hr., it deposited blackish-brown crystals, a solution of which in boiling methanol (charcoal) gave a yellow solution. Addition of perchloric acid deposited bright yellow crystals, m. p. 252° (effervescence) (E.T.) after three crystallisations from methanol (Found: C, 58·3; H, 4·5; N, 7·2%). Although the composition of this *perchlorate* is almost identical with that of the above perchlorate, m. p. 230—233°, the non-identity of the two salts is shown by their colour and their m. p.s. The infrared spectrum of the perchlorate, m. p. 252°, did not show a band corresponding to an –OH or =NH group.

(C) *The base* (VII; R = Me). A solution of this base in methanolic methyl iodide was boiled under reflux in nitrogen for 3 hr., cooled, and poured into much ether, the golden-yellow powder which separated being then collected. The yellow solution when worked up as above afforded the 1-oxo-compound (VIII), m. p. 221—223° (E.T.). The yellow powder when recrystallised from methanol (charcoal) gave the iodide (VI; X = I), m. p. 265° (E.T., I.T. 120°), which in turn gave the perchlorate (VI; X = ClO_4), m. p. 302—305° (E.T.)

The base (VII; R = Me) when treated in ethanolic solution with hydriodic acid also gave the iodide (VI; X = I), m. p. alone and mixed with the above sample, 268—275° (E.T., I.T. 215°): this iodide in turn gave the perchlorate (VI; X = ClO_4), m. p. and mixed m. p. 303° (E.T., I.T. 280°).

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412. *Infrared Absorption of Heteroaromatic and Benzenoid Six-membered Monocyclic Nuclei. Part VI.*[1] *Pyridine–Boron Complexes.*

By A. R. KATRITZKY.

The infrared spectra of the pyridine and trimethyl amine adducts of boron tri-hydride and -halides and of some substituted pyridine–boron trichloride adducts are recorded and discussed.

FOLLOWING work [1] on the characteristic ring vibrations of monosubstituted benzenes, pyridines, and pyridine 1-oxides, we have now investigated the spectra of pyridines co-ordinated with boron compounds (in these adducts a spare pair of electrons is not available for back-co-ordination into the pyridine ring; contrast pyridine 1-oxide). To facilitate assignment of the BX_3 vibrations, the spectra of trimethylamine–boron tri-hydride and -halide adducts were also determined. 0·2M-Chloroform solutions were examined in a 0·117-mm. cell.[2] Conductivity and molecular-weight measurements showed that pyridine–boron trichloride is monomeric under the conditions of measurement.[3] All the bands ($\varepsilon_A \geqslant 15$) were characteristic of the pyridine ring co-ordinately linked to boron (Tables 1 and 4), the BX_3 group (Table 3), the NMe_3 group (Table 2), or the substituent (*e.g.*, the ester bands [2b]), and tentative assignments were made as indicated in the Tables.

Trimethylamine Adducts and Boron Hydride and Halide Modes (*Tables 2 and 3*).—In unpublished work,[4] Peterson and Bauer tentatively assigned the bands in the infrared spectra (Nujol and halogenocarbon mulls and potassium bromide disks) of trimethylamine–boron tri-hydride, -fluoride, and -chloride using a normal co-ordinate analysis of the chloro-compound. This work, which came to our notice late, considerably assisted the assignments given in Tables 2 and 3. These are as in the previous work [4] except that the 1001 cm.$^{-1}$ band in trimethylamine–borine is assigned to the asymmetric C–N stretching mode instead of a BH bending mode because this band is absent in pyridine–borine. The frequencies agree well, considering the difference in states, with the above and other work, *e.g.*, the B–H stretching frequencies in borine carbonyl occur [5] at 2434 and 2380 cm.$^{-1}$, and in gaseous trimethylamine–borine [6] the B–H stretching frequency occurs at 2390 cm.$^{-1}$ and the BH_3 bending frequency at 1178—1169 cm.$^{-1}$.

Pyridine Adducts (*Table 1*).—As expected, changes in the ligand have relatively little effect on the ring vibrations. The ring-stretching frequencies (cols. 2—5) have been discussed.[1] The frequencies given in cols. 6, 8, and 9 are assigned to CH in-plane deformation modes corresponding to those in monosubstituted benzenes at *ca.* 1155, 1073, and 1028 cm.$^{-1}$, respectively.[2a] The B–N stretching frequency is considerably shifted from its position for the trimethylamine complexes but is remarkably insensitive to changes in the boron compound.

4-Substituted Pyridine–Boron Trichlorides (*Table 4*).—In the 1600—1400 cm.$^{-1}$ region the four usual ring stretching frequencies are shown (cols. 1—4). The first band occurs near 1640 cm.$^{-1}$ but is lower for the chloro-compound (cf. other series [1]); the intensity decreases as the substituent becomes more electron-attracting. The intensity of the second band, at 1570—1555 [1564 $\pm$ 5] cm.$^{-1}$,* is higher for both electron-attracting and electron-donating substituents in the 4-position than for weakly interacting groups. Another band occurs at 1511—1492 cm.$^{-1}$, except for the compounds with electron-attracting substituents; the intensity is highest for the methoxy-compound. The position of the band

* Parentheses indicate values of ε_A and square brackets arithmetical means and standard deviations.

[1] Part V, *J.*, 1958, 4162, and references therein.
[2] (*a*) Katritzky and Lagowski, *J.*, 1958, 4155; (*b*) Katritzky, Monro, Beard, Dearnaley, and Earl, *J.*, 1958, 2182.
[3] Bax, Katritzky, and Sutton, *J.*, 1959, 1258.
[4] Peterson and Bauer, "The Infrared Spectra of Lewis Salts," Cornell University report, 1955.
[5] Taylor, *J. Chem. Phys.*, 1957, **26**, 1131.
[6] Price, Frazer, Robinson, and Longuet-Higgins, *Discuss. Faraday Soc.*, 1950, **9**, 131.

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TABLE 1. *Pyridine complexes.*

		1 $A_1 + B_1$ νCH		2 A_1 νCC, νCN		3 B_1 νCC, νCN		4 A_1 νCC, νCN		5 B_1 νCC, νCN		6 B_1 βCH		7 A_1 νBN		8 B_1 βCH		9 A_1 βCH	
No.	Ligand	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A
1	BH_3	3010	20	1624	55	1580 *	10	1488	30	1459	130	(—)		1090	155	1060	10	1020	10
2	BF_3	3020	20	1630	100	1582 *	10	1493	25	1465	140	(—)		1102 †	340	1067 †	105	—	
3	BCl_3	2960	10	1636 1621	35 35	1610 *	15	1488	25	1459	130	1158	15	1095	195	—		1024	15
4	BBr_3	3080 3020	15 20	1630	115	1610 *	20	1490	50	1460	170	1160	20	1095	310	—		1025	30

TABLE 2. *Trimethylamine complexes.*

		1 CH stretch		2 CH stretch		3 CH bend		4 CH bend		5 CH bend		6 CH bend		7 BN stretch		8 CH_3 wag		9 CN stretch asym.		10 CN stretch sym.	
No.	Ligand	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A
1	BH_3	3000	45	2940	35	1483	110	1462	125	1435 *	20	1405	20	1250	30	1118	50	1001	135	851	110
2	BF_3	3030	25	2950	25	1485	125	1463	100	1452	80	1408	15	1249	160	1103 †	250	991	100	831	230
3	BCl_3	2970	15	—		1489	70	1460	100	1452 *	60	1408	25	($CHCl_3$)		1111	55	970	190	(—)	
4	BBr_3	2960	10	—		1485	90	1458	90	1449 *	60	1405	35	($CHCl_3$)		1110	65	964	180	820	150

TABLE 3. BX_3 *vibrations.*

	νBH_3 asym.		νBH_3 sym.		BH_3 bend		BH_3 wag		asym. ν $^{10}BF_3$, $^{11}BF_3$				sym. ν $^{10}BF_3$, $^{11}BF_3$				asym. νBCl_3	
	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A
Trimethylamine	2360	190	2260	110	1168	190	—		1150	430	1135 *	260	933 *	160	911	350	826	170
Pyridine	2350	165	2280 *	90	1165	170	920	25	1165	310	1125	280	912 *	240	893	430	818	55

TABLE 4. *Nuclear vibration bands.*

		1 A_1 νCC, νCN		2 B_1 νCC, νCN		3 A_1 νCC, νCN		4 B_1 νCC, νCN		5 A_1 νBN		6 A_1 βCH		7 νBCl	
No.	Substituent	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A
		4-Substituted pyridine–boron trichlorides													
1	OMe	1640 1605 *	250 45	1568	75	1511	160	1460 ‡	75	1095	250	1040	85	840 823	170 70
2	Me	1641 1606 *	160 20	1562	15	1509	30	1449	110	1092	200	1038	15	835	145
3	Et	1640	190	1560	15	1500	20	1448	155	1094	260	1052	40	843 818	75 190
4	Cl	1622	140	1555	20	1492 * 1472	60 30	1433	80	1076	270	1060 *	15	838	60
5	CO_2Et	1640	90	1570	40	—		1431	170	1076	310	1057 *	40	837 *	70
6	CO_2Me	1640	95	1567	50	—		1430	210	1077	290	1057 *	45	820	70
		4-Substituted pyridine–boron tribromide													
7	CO_2Et	1640	70	1565	45	—		1431	160	1074	410	1054	55	—	
		3-Substituted pyridine–boron trichlorides													
8	CO_2Me	1631	90	1592	25	1483	40	1441 ‡	250	1096	165	861	130	818	60
9	CO_2Et	1630	80	1590	20	1484 *	40	1440	125	1093	190	889	50	820	70

* Shoulder. ‡ Band considered to be two superimposed peaks. (—) Band hidden by other absorption. ($CHCl_3$) Band hidden by solvent. — Absence band. † Indicates that the band is strongly overlapped by BF absorption.

The symmetry type of the vibration (for approximate C_{2v} symmetry) is given directly underneath the column number in Tables 1 and 4.

at 1460—1430 cm.$^{-1}$ is lowered as the electron-accepting ability of the substituent increases; the intensity is (75—210) [(140 ± 50)].* The significance of these intensity variations has been discussed.[1]

The B–N stretching frequency (col. 5) occurs at 1095—1074 cm.$^{-1}$ (200—310) [(260 ± 35)]; its position is lowered as the electron-attracting power of the 4-substituent increases; this is as expected since the B–N bond will be weaker in these compounds. A band at 1054—1038 cm.$^{-1}$ (15—85) (col. 6) is assigned to a CH in-plane bending mode analogous to that at *ca.* 1018 cm.$^{-1}$ for *para*-disubstituted benzenes. The B–Cl stretching frequency (cf. Table 3) occurs at 843—820 cm.$^{-1}$ (60—190) (col. 7).

The nuclear bands of 4-ethoxycarbonylpyridine–boron tribromide (Table 4; No. 7) closely resemble those of the analogous trichloride, and, except for the B–N band, are included in the above ranges and statistical treatment. Table 4 also gives the nuclear bands of two 3-substituted pyridine–boron trichlorides.

Experimental.—The following were prepared as previously described.[7] 4-*Ethylpyridine*–, prisms (from ethanol), m. p. 109—111° (Found: C, 37·4; H, 3·9; N, 6·1. $C_7H_9NBCl_3$ requires C, 37·5; H, 4·0; N, 6·2%) and trimethylamine–boron trichloride (from ethanol), m. p. 237—240° (decomp.) [lit.,[8] m. p. 245° (corr.; decomp.)] (Found: C, 20·5; H, 5·3. Calc. for $C_3H_9NBCl_3$ C, 20·4; H, 5·2%).

Preparation of the other compounds has been described:[3,7] they were recrystallised or redistilled before measurement. Measurements were as previously.[1b]

I thank Dr. E. V. Ebbsworth for calling my attention to the work described in ref. 4, Professor H. J. Emeléus for making the report available to me, and Professor Bauer for permission to quote from it, Mr. E. W. Randall for conductivity measurements, and Drs. N. Sheppard and J. M. Lagowski for discussion. The work described in this and the two following papers was carried out in part during the tenure (by A. R. K.) of an I.C.I. Fellowship.

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[7] Bax, Katritzky, and Sutton, *J.*, 1958, 1254.
[8] Phillips, Hunter, and Sutton, *J.*, 1945, 146.

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413. *Infrared Absorption of Heteroaromatic and Benzenoid Six-membered Monocyclic Nuclei. Part VII.** para-*Disubstituted Benzenes.*

By A. R. KATRITZKY and P. SIMMONS.

Absorption due to the *para*-disubstituted benzene ring in 69 compounds is recorded. The variations of the positions and intensities of nine characteristic bands with the nature of the substituents are discussed. The intensities of the ring-stretching frequencies at 1600—1400 cm.$^{-1}$ depend on the charge disturbance of the ring in a manner similar to that in monosubstituted compounds.

PREVIOUSLY we showed that for monosubstituted benzenes,[1a] pyridines,[1b] pyridine 1-oxides,[1c] and pyridine–boron trichloride adducts,* the intensities of the characteristic bands depend on the nature of the substituent. Variations in the intensities of the ring stretching bands at 1600—1400 cm.$^{-1}$ have been correlated [1d] with the charge disturbance created in the ring by the substituents and/or hetero-groups. We now extend this work to polysubstituted compounds; this and the following paper deal respectively with the absorption of the *para*- and the *meta*-disubstituted benzene ring.

* Part VI, preceding paper.

[1] Katritzky and his co-workers, *J.*, 1598, (*a*) 4155, (*b*) 2198, 2202, 3165, (*c*) 2192, 2195, (*d*) 4162, (*e*) 2182.

* Shoulder. ‡ Band considered to be two superimposed peaks. (—) Band hidden by other absorption. ($CHCl_3$) Band hidden by solvent. — Absence of band. † Indicates that the band is strongly overlapped by BF absorption.
The symmetry type of the vibration (for approximate C_{2v} symmetry) is given directly underneath the column number in Tables 1 and 4.

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Problems in presenting the data arise because there are two substituents (*i.e.*, two variable parameters). Various measures of the effect of a substituent on a benzene ring are available; some examples are given in Table 1. There is no order in which substituents can be uniquely arranged; substituents can interact by inductive and mesomeric effects and have different polarisabilities, which can be invoked to a varying degree. However, on the basis of qualitatively similar effects, substituents can be divided into: (i) amino,

TABLE 1. *Mesomeric moments and sigma constants for substituent groups*

Substituent	μ_M	σ_p	σ_m	σ'	σ_R	Substituent	μ_M	σ_p	σ_m	σ'	σ_R
NMe_2 ...	1·66	−0·83	—	—	—	Me	0·35	−0·17	−0·07	−0·05	−0·13
NH_2	1·02	−0·66	−0·16	—	—	Et	—	−0·15	−0·07	—	—
OH	—	−0·37	+0·12	+0·25	−0·61	Ph	0·0	−0·01	+0·06	+0·10	−0·09
OMe ...	0·96	−0·27	+0·11	+0·23	−0·50	CN	0·45	+0·66	+0·56	+0·59	+0·07
OEt	—	−0·24	+0·1	—	—	CO_2Et ...	0·5	+0·45	+0·37	+0·32	+0·20
Cl	0·41	+0·23	+0·37	+0·47	−0·24	COMe ...	0·56	+0·50	+0·38	+0·27	+0·25
Br	0·43	+0·23	+0·39	+0·45	−0·22	NO_2	0·76	+0·78	+0·71	+0·63	+0·15

μ_M represents mesomeric moments of benzenes (cf. Everard and Sutton, *J.*, 1951, 2818, and references therein).

σ_p, σ_m, σ', and σ_R represent, respectively, Hammett's sigma *para* and *meta* constants, polar substituent constants, and resonance substituent constants (see Taft, in Newman's "Steric Effects in Organic Chemistry," Wiley, New York, 1956, p. 556 *et seq.*, and McDaniel and Brown, *J. Org. Chem.*, 1958, **23**, 420).

hydroxy, and alkoxy groups; (ii) chlorine, bromine, and iodine atoms; (iii) groups with a saturated carbon atom adjacent to the ring; (iv) those attached to the ring by an unsaturated carbon atom; (v) cyano, alkoxycarbonyl, acyl, and nitro groups. For brevity, these substituent types are denoted as follows; donor (d), halogen (x), saturated carbon (s), unsaturated carbon (u), and acceptor (a). The effect on the infrared spectrum of an unsaturated carbon substituent is similar to that of a saturated carbon substituent except when it is *para* to a (strong) donor or acceptor group (*i.e.*, conditions of high polarisation); therefore, in other environments, these types of substituents are considered together and denoted as "weak (w)." The *para*-disubstituted benzenes are arranged in Table 2 in the order: dd, dx, xx, ds, xw, ww, du, da, ua, xa, sa, aa. The order for the *meta*-disubstituted benzenes (following paper) is identical except that categories du and ua disappear, and ds and sa become dw and wa.

The spectra were measured in chloroform, and apparent extinction coefficients were recorded.[1] Solvent absorption obscured CH deformation modes below 800 cm.$^{-1}$; the concentration used was not sufficient to distinguish the combination modes at 2000—1650 cm.$^{-1}$, and the sodium chloride prism gave poor resolution in the 3000 cm.$^{-1}$ region. Thus, this work is concerned with four ring-stretching modes at 1600—1400 cm.$^{-1}$, four CH in-plane deformation modes at 1300—1000 cm.$^{-1}$, and one of the CH out-of-plane deformation modes. The bands observed are recorded in Table 2.

Randle and Whiffen [2] treated statistically the spectra of many *para*-disubstituted benzenes and listed arithmetical means and standard deviations for eight characteristic bands in the 1600—800 cm.$^{-1}$ region. They obtained data from many sources, measured under various conditions, and were unable to give precise intensities or to correlate between intensity and position of a band. McMurry and Thornton [3] give data for *para*-dialkylbenzenes, and *para*-dihalogenobenzenes have been studied in detail.[4]

Ring-stretching Frequencies (Table 2, cols. 1—4).—The first band occurs at 1616—1592 [1606 ± 6]* cm.$^{-1}$ and for certain types of compounds the range is smaller: du, da, and ua at 1608—1597 [1602 ± 3] cm.$^{-1}$; xa, sa, and aa at 1616—1604 [1610 ± 3] cm.$^{-1}$. The

[2] Randle and Whiffen, Paper No. 12, Report on Conference of Molecular Spectroscopy, 1954. Institute of Petroleum.

[3] McMurry and Thornton, *Analyt. Chem.*, 1952, **24**, 318.

[4] Stojiljković and Whiffen, *Spectrochim. Acta*, 1958, **12**, 47, 57.

second band occurs at 1590—1570 [1579 ± 6] cm.$^{-1}$ but is frequently obscured and sometimes absent. The next band is at 1522—1469 cm.$^{-1}$; the position is lowered by halogen atoms and acceptor substituents:

dd, ds, du, ww, da	1522—1504 [1511 ± 4] cm.$^{-1}$
dx, xw, ua, sa, aa	1502—1479 [1491 ± 7] cm.$^{-1}$
xx, xa	1479—1469 [1475 ± 4] cm.$^{-1}$

A last band in this region occurs frequently at 1422—1396 [1409 ± 8] cm.$^{-1}$ (but at 1392—1382 cm.$^{-1}$ for dihalogeno-compounds). These bands were previously [2] reported at [1620 ± 8 (m), 1571 ± 11 (w), 1512 ± 12 (vs), and 1450 ± 10 (m)] cm.$^{-1}$; the most serious discrepancy in position is that of the last band. Bands at 1656—1633 cm.$^{-1}$ (5) and 1521—1510 cm.$^{-1}$ (100) were reported [3] for dialkyl compounds.

para-Disubstituted benzenes with identical substituents are of V_h symmetry;† those with different substituents are of C_{2v} symmetry. The predictions [1d] concerning the intensities of the four ring-stretching frequencies of monosubstituted benzenes, pyridines, etc., of C_{2v} symmetry should therefore apply. In agreement with this, the intensity* of the A_1 vibration near 1606 cm.$^{-1}$ (I) is low when the substituents are of the same type and increases with increasing difference between the substituents. The unsaturated carbon atoms can evidently be polarised by both strong donor and strong acceptor substituents. A nitro-group *para* to another electron-accepting substituent still causes an appreciable charge disturbance in the molecule; a similar effect has been noted for ultraviolet spectra.[5]

dd, xx, xw, ww, aa‡	(0—30) [(5)]
dx, ds	(30—55) [(45 ± 10)]
xa, sa, aa′‡	(40—125) [(100 ± 20)]
du, ua	(85—240) [(175 ± 55)]§
da	(200—530) [(340 ± 100)]

The B_1 vibration near 1579 cm.$^{-1}$ (II) should show intensities that are lower than the previous band but vary with the nature of the substituents in much the same way.[1d] Although the band is often not resolved or is only partly resolved (shoulder), the band is usually more intense for compounds with substituents of different types and less intense than the preceding mode (except for the halogenonitro-compounds Nos. 50, 51).

dd, dx, xx, xw, ww, aa	(0—15) [(5 ± 5)]
ds, du, da, ua, sa	(0—95) [(30 ± 25)]

The intensity of the A_1 vibration near 1500 cm.$^{-1}$ (III) should be approximately the same as for benzene (40) for compounds with substituents that interact weakly with the ring. For other substituents it should show variations which cannot be predicted from first principles; [1d] for the monosubstituted compounds, donor substituents were found to

* Parentheses indicate apparent molecular extinction coefficients and square brackets arithmetical means and standard deviations. The intensities of shoulders and superimposed bands and the positions of shoulders are not treated statistically.

† The designation of the symmetry species of the vibration is not unambiguous for V_h molecules. In our work, as in ref. 4, yz is taken as the plane of the molecule, with the z axis passing through the substituents; in ref. 2 (published before the recommendations of *J. Chem. Phys.*, 1955, **23**, 1997) another convention has been used.

‡ Here aa indicates identical acceptor groups (Nos. 61, 62, 69), and aa′ different acceptor groups (Nos. 63—68).

§ Except No. 25 for which the intensity is (500).

[5] Schubert, Craven, Steadly, and Robins, *J. Org. Chem.*, 1957, **22**, 1285.

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TABLE 2.

			1 A_1–A_g νCC		2 B_1–B_{2g} νCC		3 A_1–B_{1u} νCC		4 B_1–B_{2u} νCC		5 B_1–B_{2g} βCH		6 A_1–A_g βCH		7 B_1–B_{2u} βCH		8 A_1–B_{1u} βCH		9 B_2–B_{2u} γCH	
			cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A
Donor–donor																				
1	NMe_2	NH_2	(—)		(—)		1513	300	—		(—)		(—)		(—)		—		816	110
2	NH_2	OMe	(—)		(—)		1510	230	—		(—)		1176	50	1122	25	(—)		822	135
3	NH_2	OEt	(—)		(—)		1510	360	(—)		(—)		1170	25	(—)		—		821	105
													1150 *	20						
4	OMe	OMe	1600	15	—		1508	270	—		(—)		1178	115	1106	45	(—)		826	150
5	OMe	OH	1607	15	—		1508	380	—		(—)		1172 ‡	230	1100	80	—		828	220
Donor–halogen																				
6	NH_2	Cl	1604 *	45	1578	10	1491	190	—		(—)		1170	45	1119	20	1004	20	819	130
7	NH_2	Br	1597	55	—		1487	185	1420	10	(—)		1171	40	1119	15	1005	30	816	100
8	OH	Cl	1592	45	(—)		1490	320	—		(—)		1170 ‡	170	(—)		1008	25	824	170
Halogen–halogen																				
9 [a]	Cl	Cl	—		—		1476	185	1392	35	—		—		1115 *	20	1012	190	819	195
10 [b]	Br	Br	—		—		1469	230	1383	55	—		—		1102	20	1005	330	810	170
Donor–saturated carbon																				
11	NH_2	Me	(—)		(—)		1512	140	—		(—)		1177	15	1122	20	—		812	110
12	OEt	Me	1615	30	1590	15	1510	145	(—)		(—)		1173	60	(—)		1005	25	818	60
13	OMe	Me	1616	55	1588	25	1510	200	—		(—)		1175	70	1110	30	(—)		818	80
Halogen–weak																				
14	Cl	Me	—		—		1491	170	(—)		—		—		1111	25	1017	55	808	115
15	Br	Me	—		—		1485	120	(—)		—		—		1110	20	1011	125	($CHCl_3$)	
16	I	Me	—		—		1482	135	(—)		1300	10	—		1110	25	1008	160	($CHCl_3$)	
17	Cl	CH:CHPy	(—)		(—)		1492	140	1408 *	40	1288	15	—		1112	25	1013	95	823	215
18	Cl	C:CPy	1603 *	165	(—)		1493	140	(—)		—		—		(—)		1013	115	828	235
19	Cl	C:CPyO	1613	5	—		1493 ‡	310	1400	20	(—)		(—)		(—)		1014	95	828 ‡	175
Weak–weak																				
20	Me	Me	—		—		1510	50	—		—		—		1119	20	1022 *	25	($CHCl_3$)	
															1102	15				
21	Me	Pr^i	—		—		1510	90	(—)		1298	10	—		1102	15	1019	15	818	100
22	Me	CH:CHPy	(—)		(—)		1510	50	(—)		1296	10	1179	25	1119	15	1016	15	818	195
23	Me	CH:CHPyO	1611	30	1573	10	1510	50	—		(—)		(—)		1113	15	1017	20	($CHCl_3$)	
24	Me	C:CPy	(—)		—		1505	15	(—)		—		1177	10	1103	15	1017	20	818 ‡	280
Donor–unsaturated carbon																				
25	NMe_2	CH:CHPyO	1601	500	(—)		1521	280	—		(—)		1182	180	1123 *	60	—		826 ‡	170
26	NH_2	3-Py	(—)		(—)		1519	85	(—)		(—)		1181	130	1127 ‡	25	(—)		832	80
27 [c]	NH_2	2-Py	(—)		(—)		1522	45	1425 *	40	(—)		1181	140	1127	15	1009	5	837	70
28	OMe	CH:CHPy	1610 *	175	1585 *	85	1512	210	(—)		(—)		1174	240	1109	20	(—)		828	190
29	OMe	CH:CHPyO	1605	230	1577	45	1508	165	1423 *	25	(—)		1168 ‡	350	1108	20	(—)		833 ‡	260
30	OMe	C:CPy	1610 *	85	1576 *	50	1509	115	(—)		(—)		1173	130	1105	30	—		831	190
Donor–acceptor																				
31	NH_2	N:NPh	1605	290	(—)		1504	115	(—)		(—)		1152 *	115	1123 *	40	—		834	150
32	NH_2	CN	1606	200	(—)		1510	120	—		(—)		1169	135	1128	15	—		827	165
																			841	95

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Donor–acceptor																				
31	NH_2	N:NPh	1605	290	(—)		1504	115	(—)		(—)		1152 *	115	1123 *	40	—		834	150
32	NH_2	CN	1606	200	(—)		1510	120	—		(—)		1169	135	1128	15	—		827	165
33	NH_2	CO_2Et	1608	275	1582 *	40	1513	60	(—)		(—)		1170	320	(—)		(—)		841	95
34	NH_2	Ac	1600	450	1574	95	1510	20	(—)		(—)		1173	225	1128	20	—		828	125
35 [d]	NH_2	NO_2	1606	320	1580 *	50	($CHCl_3$)		($CHCl_3$)		($CHCl_3$)		($CHCl_3$)		1112	155	—		($CHCl_3$)	
36	NMe_2	NO_2	1598	530	(—)		(—)		1414 *	40	(—)		1190	130	1111	440	998	40	824	195
37	OMe	NO_2	1612 *	160	(—)		1499 *	310	1420	15	(—)		1180	70	1112	250	(—)		844	230
			1598	370									1170	160						
38	OEt	NO_2	1613 *	170	(—)		1500 *	245	(—)		(—)		1170	160	1111	260	—		845	170
			1603	340																
39	OH	NO_2	1620	100	(—)		1500 *	210	—		(—)		1177	150	1112	270	—		848	180
			1603	280									1164	165						
Unsaturated carbon–acceptor																				
40	C:CPy	NO_2	1601 ‡	400	(—)		1495	80	(—)		1282	50	1174	15	1108	100	1014	25	855	230
41	C:CPyO	NO_2	1601	240	(—)		1482	200	—		(—)		(—)		1106	85	1015	35	843	240
42	CH:CHPy	NO_2	1601 ‡	380	1577 *	45	1490 *	50	(—)		1290	15	1179	20	1110	115	1008	10	839	165
43 [d]	CH:CHPyO	NO_2	1600	230	(—)		(—)		($CHCl_3$)		($CHCl_3$)		($CHCl_3$)		1109	135	1011 *	20	($CHCl_3$)	
44	CH:CH·CO_2Et	NO_2	1602	135	(—)		1491 *	50	1413	55	(—)		1183 *	240	1108	90	1012	45	845	200
45	Py	NO_2	1597	210	(—)		1481	50	1400	55	1282	20	1182	15	1105	25	1011	15	853	115
46	3-Py	NO_2	1605	170	1574 ‡	25	(—)		1396	50	1283	20	1188 ‡	25	1110 ‡	50	1018 *	15	856 ‡	220
47	2-Py	NO_2	1605	85	(—)		(—)		1405 *	10	1293	20	—		1109	50	1013	40	855	155
48	PyO	NO_2	1602	180	—		1502 *	110	1400	40	1300	40	1182 *	140	1111	100	1022	100	835 ‡	450
49 [d]	2-PyO	NO_2	1601	95	(—)		($CHCl_3$)		($CHCl_3$)		($CHCl_3$)		($CHCl_3$)		1103 ‡	10	1008	35	($CHCl_3$)	
Halogen–acceptor																				
50	Cl	NO_2	1609	110	1582	135	1479	135	1422	15	1278	20	1170	15	1109	115	1012	80	847	220
51	Br	NO_2	1609	110	1580	80	1475	100	1412	10	1271	10	1171	30	1103	55	1012	145	844	200
Saturated carbon–acceptor																				
52	Me	CN	1610	40	—		1498	10	—		—		1175	30	1117	10	1020	15	816	165
53	Me	CO_2Et	1616	115	1580	20	1501	10	1408	35	(—)		(—)		(—)		(—)		840	35
54	Me	CO_2Me	1612	90	1585	15	1502	5	1406	25	(—)		(—)		(—)		1020	70	839	40
55	Me	NO_2	1607	125	1572	20	1498 *	45	1419	10	1297	20	1177	35	1109	90	1016	20	835	130
56	CH_2Py	NO_2	(—)		(—)		1493 *	35	—		—		1180	15	1111	40	1106	20	(—)	
57	CH_2Py-2	NO_2	1603 *	100	(—)		1489	45	(—)		—		1177	20	1108	70	1014	30	827	30
58	CH_2PyO	NO_2	1608	115	(—)		(—)		(—)		(—)		(—)		1110	70	1017	30	(—)	
59	CH_2PyO-2	NO_2	1609	120	(—)		(—)		1419 *	85	(—)		(—)		1112 ‡	80	1018	40	(—)	
60	CH_2Cl	NO_2	1609	85	1570	15	1492	35	1410	15	1264	85	1176	15	1109	70	1015	25	(—)	
Acceptor–acceptor																				
61	CO_2Me	CO_2Me	—		1580	15	1501	15	1410	100	(—)		1150 *	30	1106 ‡	275	1020	165	838	10
62	CO_2Et	CO_2Et	1613	15	1585	15	1500	15	1408	120	(—)		(—)		(—)		(—)		842	25
63	CN	NO_2	1610	90	—		1490 *	30	—		1290	65	—		1106	35	1017	35	857 ‡	310
64	CO_2Me	NO_2	1612	75	—		(—)		1410	20	(—)		1167 *	15	1103 *	180	1015	85	857	90
65	CO_2Et	NO_2	1608	80	1578 *	15	(—)		1410	40	(—)		1168	30	1109 *	165	(—)		839	120
66	CHO	NO_2	1610	115	1585 *	10	(—)		—		1293	75	1162	15	1106	35	1012	35	(—)	
67	COMe	NO_2	1604	115	(—)		(—)		1408 *	35	(—)		—		1105	25	1011	50	853 ‡	250
68	COPy-2	NO_2	1609	105	(—)		—		1406	35	(—)		1156	45	1106	25	1015	25	851	190
69	NO_2	NO_2	—		(—)		1479	30	1402 *	20	(—)		—		1102	60	1011	60	836	400

Assignments for symmetry (both C_{2v} and V_h) and vibration type are given immediately below the column number (cf. ref. 2).

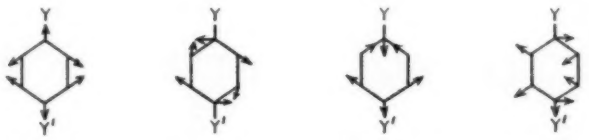
* Shoulder. ‡ Absorption considered to be the superimposition of two peaks, — absence of absorption, (—) bands masked by stronger absorption, ($CHCl_3$) band masked by solvent, Py pyridyl radical (number indicates position of linkage, unless this is 4), PyO substituted pyridine oxide.

(*a*) Combination bands at 1632 (10) and 1420 cm.$^{-1}$ (10) (cf. ref. 4). (*b*) Combination bands at 1628 (10), 1495 (20), 1408 (10), and 1136 cm.$^{-1}$ (10) (cf. ref. 4). (*c*) A band at 1448 cm.$^{-1}$ (150) is probably due to the 2-pyridyl nucleus rather than the shoulder at 1425 cm.$^{-1}$ as previously reported.[1] (*d*) Measured in a 1-mm. cell.

increase and attractor substituents to decrease the intensity. This is the case here also:

dd, dx, xx	(185—380) [(265 ± 75)]
ds, xw, xa	(100—200) [(140 ± 25)]
ww	(15—90) [(50 ± 25)]
sa, aa	(0—45) [(20 ± 15)]

except that the intensity is very irregular for those compounds in which the substituents interact strongly: du, da, ua (20—280) [(120 ± 75)].



(I) A_1 (A_g) (II) B_1 (B_{1g}) (III) A_1 (B_{2u}) (IV) B_1 (B_{3u})

The intensity of the B_1 vibration near 1409 cm.$^{-1}$ (IV) should be approximately (40) and not vary regularly with the electron-donor or -acceptor ability of the substituents.[1d] Agreement is least satisfactory in this case. This region of the spectrum is obscured by substituent absorption for 31 compounds, and for 8 of these this band appears as a shoulder. Of the remaining compounds, 18 showed no band, and 20 absorb with intensity (10—55) [(30 ± 15)] except that it is higher (100—120) for alkoxycarbonyl compounds. Compounds with electron-accepting substituents tended to show more intense absorption; this was also noticed with monosubstituted compounds.[1d]

In-plane CH *Bending Vibrations* (Table 2, cols. 5—8).—Absorption at 1300—1264 cm.$^{-1}$ (15—85) [1285 ± 11 cm.$^{-1}$ (35 ± 25)] for most of the ua, xa, sa, and aa compounds is presumably the B_1–B_{3g} mode, previously expected, but not found,[2] near 1290 cm.$^{-1}$.

The A_1–A_g mode occurs at 1190—1164 [1175 ± 6] cm.$^{-1}$ except that for aa compounds the frequency is depressed to 1168 1156 [1162 ± 6] cm.$^{-1}$. The intensity depends on the substituents present:

du, da	(130—320) [(175 ± 60)]
dd, dx, ds	(15—115) [(50 ± 30)]
xx, xw	band absent
all others	(0—45) [(15 ± 10)]

The B_1–B_{2u} vibration absorbs at 1128—1100 [1111 ± 7] cm.$^{-1}$. The intensity varies with the type of substituents present:

dd, dx, xx, ds, xw, ww, du	(15—80) [(25 ± 15)]
da	(155—440) [(275 ± 85)], when a is the nitro-group; otherwise (15—20)
ua, xa, sa, aa	(10—135) [(65 ± 35)]

The A_1–B_{1u} mode occurs at 1022—1004 [1013 ± 5] cm.$^{-1}$; the intensity depends on the substituents:

xx	(190—330)
xw, xa	(55—160) [(110 ± 35)]
ua, sa, aa	(10—165) [(45 ± 35)]
dx, ds, ww	(0—30) [(15 ± 10)]
dd, du, da	absent

The last three bands were previously reported [2] at [1179 ± 7 (s), 1125 ± 10 (var), and 1018 ± 10 (s)] cm.$^{-1}$. Bands were found [3] for *p*-dialkylbenzenes at 1230—1195 cm.$^{-1}$ (5), 1205—1175 cm.$^{-1}$ (5), 1130—1090 cm.$^{-1}$ (20), 1070—1035 cm.$^{-1}$ (20), and 1030—1010 cm.$^{-1}$ (10). The positions and intensities of the A_1–B_{1u} band near 1013 cm.$^{-1}$ given by Randle and Whiffen [6] for several compounds agree reasonably with the present results; for this band, it was shown [5] that for *p*-halogenomethyl- and *p*-dihalogeno-benzenes, the band intensity increased with the mass sum of the substituents.

Out-of-plane CH *Bending Mode* (Table 2, col. 9).—The B_2–B_{3u} mode is shown at 828—808 [819 ± 6] cm.$^{-1}$ for compounds in classes dd ⟶ ww (Nos. 1—24) (except for Nos. 15, 16, 20, and 23 where the band is apparently masked by solvent absorption below 805) and at 857—824 [841 ± 10] cm.$^{-1}$ for the other compounds (except for No. 52 with a frequency of 816 cm.$^{-1}$; the cyano-group often does not behave as a strong electron acceptor; cf. ref. 1). The intensity is (60—240) [(155 ± 50)] for compounds in classes dd ⟶ xa (Nos. 1—51), but for compounds of the sa class it is often much lower (30—165), and in the aa class the intensity is very high for the dinitro-compound (No. 69), very low for the dialkoxycarbonyl compounds (Nos. 61, 62), and intermediate for the others.

This band has been much studied previously. Ranges of [817 ± 13 (vs)],[2] 833—810 (200),[3,7] and 860—800 cm.$^{-1}$ [8] have been suggested. Many individual values for the band position have been quoted (see, *e.g.*, refs. 9—11) which generally agree well with our values. Attempts have been made to correlate the positions of the band with Hammett's σ values [10] and with shifts observed in monosubstituted benzenes.[11]

Substituent Bands.—With few exceptions, all other bands of $\varepsilon_A \geqslant 15$ for these compounds could be assigned to the substituents. Those for pyridine and pyridine 1-oxide rings have already been published.[1]

Experimental.—The preparations of the compounds containing a pyridine or pyridine 1-oxide ring have been given elsewhere.[1,12] The other compounds were commercial products or were prepared by standard methods. All compounds were recrystallised or redistilled immediately before measurement and had melting or boiling points in agreement with literature values.

The spectra were measured on the Oxford Perkin–Elmer 21 spectrophotometer with a sodium chloride prism, slit programme 4, and the settings previously reported.[1c] ε_A values were calculated as before (see ref. 1*a*).

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[6] Randle and Whiffen, *Trans. Faraday Soc.*, 1956, **52**, 9.
[7] Jones and Sandorfy, in Weissburger, "Techniques of Organic Chemistry, Vol. IX. Chemical Applications of Spectroscopy," Interscience Publ. Inc., London 1956, p. 391.
[8] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1958, 2nd Edn., p. 65; Colthup, *J. Opt. Soc. America*, 1950, **40**, 397.
[9] Whiffen and Thompson, *J.*, 1945, 268; Bell, Thompson, and Vago, *Proc. Roy. Soc.*, 1947, *A*, **192**, 498; Cole and Thompson, *Trans. Faraday Soc.*, 1950, **46**, 103.
[10] Bellamy, *J.*, 1955, 2818.
[11] Margoshes and Fassell, *Spectrochim. Acta*, 1955, **7**, 14.
[12] Hands and Katritzky, *J.*, 1958, 1754.

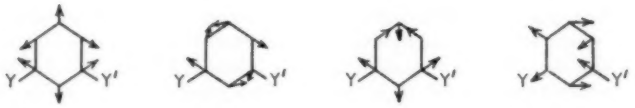
414. *Infrared Absorption of Heteroaromatic and Benzenoid Six-membered Monocyclic Nuclei. Part VIII.*[1] meta-*Disubstituted Benzenes.*

By A. R. Katritzky and P. Simmons.

Absorption due to the *meta*-disubstituted benzene ring is recorded and discussed for 43 compounds.

Following work on *para*-disubstituted benzenes,[1] we now report on 43 *meta*-disubstituted compounds (Table 1). The object of the work, the conditions of measurement, the regions of the spectrum investigated, and the arrangement of the tables are discussed in the preceding paper,[1] and the notes therein on substituent bands and experimental details also apply to this work.

Ring Stretching Frequencies at ca. 1600—1400 cm.$^{-1}$ (Table 1, cols. 1—4).—The first band occurs at 1622—1610 [1616 ± 4] cm.$^{-1}$ for compounds containing a strongly electron-attracting group (Nos. 22—43 †), at 1580—1572 cm.$^{-1}$ when two halogens are present



(I) A_1 (II) B_1 (III) A_1 (IV) B_1

(Nos. 9, 10), and at 1611—1597 [1603 ± 4] cm.$^{-1}$ for the other compounds. A second band occurs at 1595—1575 [1586 ± 5] cm.$^{-1}$ except for the dinitro-compound (No. 43). The third band is at 1460 cm.$^{-1}$ when two halogens are present (Nos. 9, 10); the position is 1495—1471 cm.$^{-1}$ for the other compounds, but tends to lower frequencies as the electron-attracting ability of the substituents increases:

Nos.	1—8, 11—19	20—35	36—43
Range	1495—1479	1483—1475	1478—1471 cm.$^{-1}$
Mean and deviation	1489 ± 5	1480 ± 3	1475 ± 3 cm.$^{-1}$

The intensities of these bands depend on the substituents present (Table 2).

The fourth band in this region occurs at 1467—1447 [1458 ± 7] cm.$^{-1}$ for compounds containing a donor group, a halogen atom, or two weak groups (Nos. 1—8 and 11—27), and at 1443—1430 [1437 ± 6] cm.$^{-1}$ for other compounds (Nos. 28—43), except that the dihalides (Nos. 9, 10) absorb at 1413—1410 cm.$^{-1}$. This band is frequently obscured, and the intensities are irregular (5—65) [(35 ± 20)].

Randle and Whiffen [2] reported these bands at [1611 ± 9 (s), 1590 ± 7 (s), 1499 ± 7 (vs), and 1447 ± 15 (m)] cm.$^{-1}$; these positions are in reasonable agreement with our results except for the third band. Our assignment of the bands to vibrations (I)—(IV), respectively, although slightly different from the previous one,[2] appears to explain the intensity variations better (see below).

Alterations in the charge density of a ring by the mesomeric effect of a substituent are

† Except No. 33 where the low frequency is probably partly due to overlap with a heterocyclic nuclear band.

[1] Katritzky and Simmons, preceding paper.
[2] Randle and Whiffen, Paper No. 12, Report on Conference of Molecular Spectroscopy, 1954, Institute of Petroleum.

greatest in the *ortho*- and *para*-positions. Thus, *meta*-substituents of the same and opposite type respectively reinforce and lessen charge disturbance. Vibrations (I) and (II) (Table 1, cols. 1 and 2) should show intensities proportional to the amount of charge disturbance in the ring,[3] and this is so (Table 2) (donor groups appear to disturb the charge symmetry more than acceptor groups,[3] and weak groups are weak electron donors). For monosubstituted compounds the vibration analogous to (III) is intensified by electron-donor substituents,[3] and this is also true in the present series (Table 1, col. 3; Table 2). The intensity of the fourth band (Table 1, col. 4) shows little dependence on the substituent type, as expected.[3]

In-plane Hydrogen Deformation Modes (Table 1, cols. 5—8).—A band which occurs at 1297—1262 cm.$^{-1}$ (5—50) [1278 ± 12 cm.$^{-1}$ (30 ± 15)] for 13 compounds is absent for four others, and the region is obscured by substituent absorption for the remainder.

A band or shoulder at 1192—1181 cm.$^{-1}$ for nine compounds {for Nos. 1—6 and 12—14, respectively: 1181 (35) 1192 (35), 1183 (190), 1190 (70), 1180 (285), 1185* (85), 1186 (55), 1190* (25), 1182 (65)} appears to be a subsidiary of the band at 1157 ± 5 cm.$^{-1}$. The intensity of the band at 1166—1149 [1157 ± 5] cm.$^{-1}$ (col. 6) is enhanced by the presence of strong electron-donor groups, particularly alkoxyl and hydroxyl:

Nos.	4, 5, 6	2, 3	12, 13, 14	1	7, 8, 11	9, 10, 15—43
Subst.	OR, OR	OR, NH_2	OR, Me	NH_2, NH_2	NH_2 with Me, Cl, or Br	others
ε_A	310—440	165—280	150—155	110	25—50	⩽25

Compounds with a strong electron-attracting group, two weak groups, or two halogen atoms (Nos. 9, 10, 20—43) show a band (col. 7) at 1109—1082 cm.$^{-1}$ (10—75) [1096 ± 7 cm.$^{-1}$ (30 ± 15)]. Another band (col. 8) is found at 1091—1061 [1076 ± 7] cm.$^{-1}$. The intensity is high (60—135) for compounds containing two nitro-, ethoxycarbonyl-, or methoxycarbonyl-groups (Nos. 34, 35, 37, 38, 43) and moderate (20—50) [(30 ± 10)] for compounds containing one of these groups (Nos. 22—33, 36, 39—42); the band appears (⩽45) for five of the ten other compounds in which the region is not obscured by substituent absorption.

Randle and Whiffen [2] expected, but did not find, the first βCH frequency (Table 1, col. 5) at >1200 cm.$^{-1}$; they reported other bands at [1165 ± 6 (var.), 1081 ± 10 (m), and 1045 ± 7 (m) cm.$^{-1}$]. Agreement with the present work is good for the first and the second band, but instead of the band near 1045 cm.$^{-1}$, we find absorption near 1096 cm.$^{-1}$. McMurry and Thornton report [4] bands at 1200—1155 cm.$^{-1}$ (10), 1185—1150 cm.$^{-1}$ (10), 1120—1085 cm.$^{-1}$ (10), and 1060—1030 cm.$^{-1}$ (10) for *meta*-dialkylbenzenes.

Ring-breathing Frequency (Table 1, col. 9).—Twenty-five of the compounds absorb at 1002—990 cm.$^{-1}$ (5—70) [995 ± 3 cm.$^{-1}$ (20 ± 15)], and the band is absent for nine compounds; it was previously reported [2] at [999 ± 5] cm.$^{-1}$ (var).

Out-of-plane Hydrogen Deformations (Table 1, cols. 10—12).—Compounds with two strong donor groups absorb in the 950 cm.$^{-1}$ region {for Nos. 1—6 respectively 952 (25), 940 (25), 960* (10), 920* (15), 977* cm.$^{-1}$ (20), (—)}. A band at 930—903 [914 ± 8] cm.$^{-1}$ is shown by most compounds with an electron-attracting group and some others. The intensity is (5—45) [(20 ± 10)], except for the dinitro-compound (No. 43). Another band occurs at 841—828 [836 ± 5] cm.$^{-1}$ for donor–donor compounds (Nos. 1—6) and at 903—862 [880 ± 11] cm.$^{-1}$ otherwise; the intensity is (10—95) [(40 ± 25)]. Absorption is sometimes shown just above the solvent cut-off at 805 cm.$^{-1}$.

These bands were previously reported [2] at [964 ± 10 (w), 904 ± 13 (var), 876 ± 10 (vs), and 782 ± 9 (vs)] cm.$^{-1}$, respectively. The second and the third band were found [4] for *meta*-dialkylbenzenes at 930—880 cm.$^{-1}$ (10) and 895—860 cm.$^{-1}$ (20). An attempt has

[3] Katritzky, *J.*, 1958, 4162.
[4] McMurry and Thornton, *Analyt. Chem.*, 1952, **24**, 318.

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TABLE 1.

			1 A_1 νCC		2 B_1 νCC		3 A_1 νCC		4 B_1 νCC		5 B_1 βCH		6 B_1 βCH		7 A_2 βCH		8 B_1 βCH		9 A_1 ring		10 A_2 γCH		11 B_2 γCH		12 B_2 γCH	
			cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A
Donor–donor																										
1	NH_2	NH_2	1600 *	205	(—)		1495	110	(—)		—		1159	110	—		—		—		—		834	85	—	
2	NH_2	OMe	1607	220	(—)		1493	210	(—)		(—)		1170	90	—		1072 *	25	992	5	—		841	50	—	
													1156	280									828	55		
2	NH_2	OEt	1602	220	1590 *	160	1492	150	1460 *	60	(—)		1158	165	(—)		(—)		992	5	—		839	40	—	
													1152 *	160									817 *	20		
4	OMe	OMe	1597	270	(—)		1490	250	1459 †	135	(—)		1161 *	110	—		1079	45	990	10	905	45	850 *	20	—	
													1150	440									835	70		
																							822	25		
5	OEt	OEt	1602	220	1592 *	200	1489	155	(—)		(—)		1151	310	(—)		(—)		992 *	20	905	10	859 *	20	—	
																							841	30		
																							820	20		
6	OMe	OH	1605	250	(—)		1495	200	1464 †	85	(—)		1169	95	(—)		1078	30	996	10	922	20	850 *	15	—	
													1149	360									837	50		
																							820 *	15		
Donor–halogen																										
7	NH_2	Cl	1603	210	(—)		1484	150	1450	40	1297	30	1161	25	—		(—)		993	55	—		888	95	—	
																							848	65		
8	NH_2	Br	1597	180	1586	110	1480	210	1447	50	1295	25	1160	35	—		(—)		990	70	—		872 *	35	—	
																							862	85		
																							848 *	65		
Halogen–halogen																										
9	Cl	Cl	1580	185	(—)		1460	165	1413	40	1285	5	1155	10	1109	25	1071 *	70	997	15	—		867	60	—	
									1400 *	30																
10	Br	Br	1572	175	(—)		1460	90	1410	30	—		1150	5	1098	15	(—)		992	25	—		869	25	—	
									1398 *	25																
Donor–weak																										
11	NH_2	Me	(—)		1594 *	85	1491	85	1467	30	(—)		1166	50	—		—		993	10	919	5	868 *	15	—	
12	OEt	Me	1602	90	1585	95	1487	90	(—)		(—)		1168	90	(—)		(—)		1000	50	(—)		875	15	—	
													1155	155												
13	OMe	Me	1608	120	1590	90	1490	130	1467 †	70	1300 *	30	1163	100	—		1083	10	994	20	910	20	895	10	—	
													1152	150									874	10		
14	OH	Me	1616 *	65	1595	110	1488	70	1460	35	1263 *	45	1150	150	—		1080	15	999	15	925	40	876	10	—	
15	OMe	$CH{:}CH{\cdot}CO_2Me$	1603	110	1586	140	1488	90	1460 †	90	(—)		(—)		—		1081	15	(—)		913	15	872 *	20	—	
16	OMe	$CH{:}CH{\cdot}CO_2Et$	1600 *	110	1585	140	1487	105	(—)		(—)		(—)		(—)		1081 *	30	(—)		—		880 *	10	—	
17	NH_2	4Py	1601 †	360	(—)		1479	60	1451	30	(—)		1165	15	—		—		997 †	50	—		863	30	—	
18[a]	NH_2	2-Py	(—)		(—)		1498 *	20	1450 *	45	(—)		(—)		(—)		(—)		992 †	40	—		883	25	—	
							1478 *	70															865	25		
19	NH_2	2-PyO	(—)		1590 *	110	(—)		1452 *	20	1296	40	—		(—)		—		993	20	—		893	60	—	
																							868	30		
Halogen–weak																										
20[b]	Cl	Me	1600	50	1578	40	1476	80	(—)		—		1160	5	1098	20	(—)		995	10	—		868	20	—	
Weak–weak																										
21	Me	Me	1611	40	1596 †	20	1483	35	(—)		—		1165	10	1094	15	—		—		903	10	880	10	—	

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Donor–acceptor																								
22	NH_2	NO_2	(—)		1587	50	1482	60	1460 *	20	(—)		1159	10	1108	20	1091	30	994	20	927	10	888	10	813	120)
23	OEt	NO_2	1620	65	1581	55	1482	75	(—)		(—)		1152	10	1094 †	75	1078 *	30	996	10	—		870	55	(805	70
24	OMe	NO_2	1620	50	1582	50	1482	95	1448 *	50	(—)		1181 *	30	1092	45	1073	25	994	15	—		896	15	(795	50)
																							875	25		
25	OH	NO_2	1622	50	1592	35	1476	35	1452	35	(—)		1157 *	55	1087	20	1071	25	999	20	928	30	874	35	812	145
Halogen–acceptor																								
26	Cl	NO_2	1602 *	15	1582	20	(—)		1462	40	1265	20	—		1095	10	1065	50	—		917	10	888	65	—	
27	Br	NO_2	1598 *	10	1578 *	10	1500 *	35	1464	45	1267	25	—		1125 *	25	1061	50	998	15	918	5	888	45	—	
															1094	20										
Weak–acceptor																								
28	Me	CO_2Et	1610	25	1592	40	(—)		(—)		(—)		1165 *	25	(—)		1082 †	110	1003 *	20	910	10	862	10	—	
29	Me	CO_2Me	1610	30	1594	45	1481 *	15	(—)		(—)		—		(—)		1084 †	95	1000	35	—		870	10	—	
30	Me	NO_2	—		1587 *	15	1482	35	(—)		1289 *	20	—		1096	40	1080	25	—		906	25	880	15	(798	35)
31	CH_2Cl	NO_2	1615	10	1587	15	1480	30	1442	20	1262	50	—		1097	40	1074	25	—		910	10	—		(807	65)
32	4Py	NO_2	1617 *	50	1593 *	55	1475	20	1436	10	1288	25	—		1103	20	1083	20	1001 *	15	905	30	879 †	90	(802	65)
											1270	30														
33	2PyO	NO_2	1605	35	(—)		(—)		1442	65	(—)		(—)		1100	45	1085 *	15	—		906	25	886 †	90	(803	20)
Acceptor–acceptor																								
34	CO_2Me	CO_2Me	1612	30	1590	15	1482	15	(—)		(—)		(—)		(—)		1078	105	(—)		—		—		($CHCl_3$)	
35	CO_2Et	CO_2Et	1610	45	1588	45	1475 *	45	(—)		(—)		(—)		(—)		1076	135	1003 *	50	916	20	(—)		($CHCl_3$)	
36	CN	NO_2	1620	45	1580 *	15	1473	15	1430	5	1279	15	1160	5	1095	30	1075	20	—		905	45	902 *	45	806	50
37	CO_2Me	NO_2	1618	70	1587 *	15	1478	55	(—)		(—)		(—)		1082	35	1068	60	—		919	15	892	35	818	40
38	CO_2Et	NO_2	1620	65	1587 *	10	1478	60	1440 †	45	(—)		1170 *	30	1094 †	75	1068	60	1002 *	30	920	20	910 *	15	816	20
39	COCl	NO_2	1618	115	1584	20	1471	20	1431	20	1278	40	1162 *	15	1094 *	70	(—)		1000	10	916 *	60	—		809	40
40	CHO	NO_2	1618	120	1583	35	1478	40	1443	30	1283	50	1157	15	1083	60	1071 *	40	1002	10	930	40	903	50	817	70
41	COMe	NO_2	1613	105	1575	25	1473	60	1428 †	55	1275	50	1157	20	1109	75	1070	35	997	10	912	15	898	35	808	40
42	CO·Py-2	NO_2	1618	110	1575 *	60	1477	45	(—)		1274 *	5	(—)		1094 †	110	(—)		(—)		908	20	871	55	820	50
43	NO_2	NO_2	1618	110	1608	140	1470 *	15	—		1266	70	1158	25	1091	35	1065	120	—		913	85	903	70	808	60

Assignments for symmetry and vibration type are given immediately below the column number (cf. Ref. 2).

* Shoulder. † Absorption considered to be the superimposition of two peaks, — absence of absorption, (—) bands masked by stronger absorption, ($CHCl_3$) band masked by solvent, Py pyridyl radical (number indicates position of linkage), PyO substituted pyridine 1-oxide.

(*a*) Band at 1462 cm.$^{-1}$ (175) is now considered to be due to the 2-pyridyl nucleus in place of that at 1478 * (70), cf. Katritzky and Hands, *J.*, 1958, 2202.

(*b*) Extra band at 855 (85).

TABLE 2. ε_A *Values.*

Nos.		Band near 1600 cm.$^{-1}$ Range	Band near 1600 cm.$^{-1}$ M and α *	Band near 1580 cm.$^{-1}$ Range	Band near 1580 cm.$^{-1}$ M and α *	Band near 1480 cm.$^{-1}$ Range	Band near 1480 cm.$^{-1}$ M and α *
1—10	Donor–donor, Donor–halogen, Halogen–halogen	175—270	215 ± 30	90—140	115 ± 20	90—250	170 ± 50
11—19	Donor–weak	90—120	105 ± 15			60—130	90 ± 20
20—25	Halogen–weak, Weak–weak, Donor–acceptor	40—65	50 ± 10	35—55	45 ± 10	35—95	65 ± 25
26—33	Halogen–acceptor, Weak–acceptor	0—35	20 ± 15	15—45 *	30 ± 10	20—35	30 ± 5
34—43	Acceptor–acceptor	30—120	80 ± 35			15—60	40 ± 20

* Except No. 43, see text.

* M and α, Arithmetical mean and standard deviation.

been made [5] to correlate a band at 906—838 cm.$^{-1}$ with the sum of Hammett's *meta*-sigma constants for the substituents.

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[5] Bellamy, *J.*, 1955, 2818.

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415. *Infrared Absorption of Substituents in Aromatic Systems. Part I. Methoxy- and Ethoxy-compounds.*

By A. R. KATRITZKY and N. A. COATS.

The absorption bands caused by the methoxyl group in twenty-three compounds, and the ethoxyl group in fifteen compounds, are recorded and discussed.

KATRITZKY and his co-workers [1-3] have shown that a heteroaromatic or benzenoid ring substituted in the same position(s) possesses characteristic bands, the frequencies and intensities of which are either reasonably constant or vary in a regular manner with the electronic nature of the substituent. The remaining bands of $\varepsilon_A \geqslant 15$ are (with few exceptions) characteristic of the substituent and are also reasonably constant or show variations of intensity and/or position which can be correlated with the nature of the ring.

Details of these bands have been published for some carbonyl compounds; [1] this series will deal with other substituents. In this paper the absorption caused by methoxyl and ethoxyl groups is reported. For conditions of measurement, the justification for recording apparent extinction coefficients, and the errors and approximations involved therein, see ref. 1. The results are given in Tables 1 and 2.

Although dimethyl ether has been studied in detail,[4] relatively little has been reported for aromatic ethers.[5-9] In the most extensive investigation before the present work, Briggs *et al.*[9] measured eleven methoxy- and three ethoxy-compounds (as mulls, films, or in potassium bromide or carbon tetrachloride) and proposed several characteristic bands for each group. The results of the previous workers are compared below with our conclusions.

The 3000 *cm.*$^{-1}$ *Region.*—The symmetric methyl CH stretching frequency of methyl ethers was previously [8] reported at 2832—2815 cm.$^{-1}$ (calcium fluoride prism), and even with the poor resolution of the sodium chloride prism a band or shoulder is shown for the benzenoid methoxy-compounds at *ca.* 2850 cm.$^{-1}$; for the heterocyclic derivatives, this region is usually obscured by the CH stretching of the hydrogen-bonded solvent [2a] (Table 1, col. 1).

The 1500—1350 *cm.*$^{-1}$ *Region.*—Bands are found at 1468—1458 cm.$^{-1}$ (50—80) [1463 ± 3 cm.$^{-1}$ (60 ± 10)] * and 1445—1432 cm.$^{-1}$ [1440 ± 4 cm.$^{-1}$] for the methoxy-compounds (Table 1, cols. 2 and 3). The intensity of the latter band is (30—60) [(40 ± 10)]

* Apparent extinction coefficients are enclosed in parentheses and standard deviations in brackets (cf. ref. 1). The intensities of shoulders and superimposed bands and the positions of shoulders are not treated statistically.

[1] Cf. Katritzky, Monro, Beard, Dearnaley, and Earl, *J.*, 1958, 2182.
[2] (*a*) Katritzky and Gardner, *J.*, 1958, 2198; Katritzky and Hands, *ibid.*, pp. 2195, 2202; Katritzky, Hands, and Jones, *ibid.*, p. 3165; Katritzky and Gardner, *ibid.*, p. 2192; Katritzky, *J.*, 1959, 2049; Katritzky, Beard, and Coats, unpublished work. (*b*) Katritzky and Lagowski, *J.*, 1958, 4155.
[3] Katritzky, *J.*, 1958, 4162.
[4] Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," Van Nostrand, Princeton, 1945, p. 353.
[5] Lecomte in "Traité de Chimie Organique," edited by Grignard, Masson et Cie, Paris, 1936, Vol. II, p. 238; Jones and Sandorfy in Weissburger, "Technique of Organic Chemistry," Interscience Publ. Ltd., London, 1956, Vol. IX, p. 435.
[6] Colthup, *J. Opt. Soc. America*, 1950, **40**, 397.
[7] Tschamler and Leutner, *Monatsh.*, 1952, **83**, 1502.
[8] Henbest, Meakins, Nicholls, and Wagland, *J.*, 1957, 1462.
[9] Briggs, Colebrook, Fales, and Wildman, *Analyt. Chem.*, 1957, **29**, 904.

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for the benzenoid compounds (Nos. 1—16) but appreciably higher (70—110) for the heterocyclic compounds. Absorption occurs at 1480—1471 cm.$^{-1}$ (35—115) [1476 ± 3 cm.$^{-1}$ (80 ± 20)], 1448—1442 cm.$^{-1}$ (20—35) [1444 ± 2 cm.$^{-1}$ (25 ± 5)], and 1398—1385 cm.$^{-1}$ (35—110) [1392 ± 3 cm.$^{-1}$ (60 ± 20)] for the ethoxy-compounds (Table 2, cols. 1, 2, and 3). These bands have been assigned (see Tables) by comparison with the corresponding esters.

TABLE 1. *Methoxy-compounds.*

		1		2		3		4		5		6	
		CH_3		CH_3 bending									
		νCH		asym.		sym.		COC asym. stretch				COC sym. stretch	
No.	Ring	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A
1	Ph	2835	20	1466	50	1441 *	40	{1301 1290 *	55 45	1244	250	1039	130
2	$C_6H_4{\cdot}NH_2$-*m*	2850 *	15	1460	70	1440	40	1300 *	55	1288	100	1038	120
3	$C_6H_4{\cdot}OMe$-*m*	2830	*45*	1459 †	*135*	1437	*100*	(—)		{1282 1262	*150* *140*	{1048 1032	*160* *110*
4	$C_6H_4{\cdot}OH$-*m*	2860	15	1464 †	85	1442	60	1329	65	1286	135	1040	105
5	$C_6H_4{\cdot}Me$-*m*	2850	20	1467 †	75	1436	35	1290	90	1260	150	{1054 1042	70 80
6	$C_6H_4{\cdot}CH{:}CH{\cdot}CO_2Me$-*m*	2840	20	1460 †	90	1438 †	145	1273 *	215	1260 *	235	1041	135
7	$C_6H_4{\cdot}CH{:}CH{\cdot}CO_2Et$-*m*	2850 *	20	1465 †	110	1432 ‡	80	(—)		1257 *	250	1040 †	180
8	$C_6H_4{\cdot}NO_2$-*m*	2840 *	15	1458	55	1440 *	40	1283	155	1246	240	{1040 * 1035	100 110
9	$C_6H_4{\cdot}NH_2$-*p*	2850	15	1468	50	1443	35	{1327 1293	15 30	(1236	230)	1035	115
10	$C_6H_4{\cdot}OMe$-*p*	2850	*40*	1464	*100*	1442	*80*	1291	*35*	(1225	*270*)	1042	*220*
11	$C_6H_4{\cdot}OH$-*p*	2840	25	1467	80	1436 †	90	1294	45	($CHCl_3$)		1034	170
12	$C_6H_4{\cdot}Me$-*p*	2840 *	25	1465	55	1442 *	40	1293	75	1242	210	1033	105
13	$C_6H_4(CH{:}CH{\cdot}4P)$-*p*	2850 *	20	1465	55	1445	30	{1325 * 1280	15 130	1252	290	1034	125
14	$C_6H_4(CH{:}CH{\cdot}4PO)$-*p*	2855 *	25	1465 *	120	1450 *	75	{1330 * 1275 *	20 145	1247 †	450	1028 †	230
15	$C_6H_4(C{\vdots}C{\cdot}4P)$-*p*	2850 *	30	1463	50	1442	35	{1315 * 1286	25 145	1247	310	1029	130
16	$C_6H_4{\cdot}NO_2$-*p*	2850	25	1459	80	1442	50	1295	105	1262	490	1028	190
17	4P	(—)		1466	75	1445	90	—		1288	260	1033	205
18	2P	(—)		1470 *	45	1445	110	1312	145	{1292 1248	260 105	{1045 † 1020	110 115
19	4PO	(—)		1464	60	1440 †	135	—		1292	210	1027 †	290
20	4PO(3Me)	(—)		1460 *	105	1442 *	115	1300	50	1283	310	1028	280
21	3PO	(—)		1460	70	1438 †	160	—		1308	165	1043	115
22	2PO	(—)		1459 *	70	1440 *	85	—		{1311 1273	290 170	1023	175
23	$4PBCl_3$	—		1466 †	75	1440	70	1331 *	55	1313	220	1013	100

* Shoulder. † Absorption considered to be the superimposition of two peaks. — Absence of absorption. (—) Band masked by stronger absorption. ($CHCl_3$) Band masked by solvent. ‡ Band the intensity of which is markedly raised by overlap.

Ph phenyl, P substituted pyridine, PO substituted pyridine 1-oxide, PO(3Me) substituted 3-methylpyridine 1-oxide; the position of the substituent is indicated by a numeral.

ε_A values in italics indicate absorption by two alkoxyl groups in similar environments.

Unexplained bands ($\varepsilon_A \geqslant 15$) were shown for compound No. 19 at 2470 (25) and 1567 (25) cm.$^{-1}$; for No. 17 at 1633 (30) and 837 (55) cm.$^{-1}$; for No. 21 at 1080 (15) cm.$^{-1}$; and for No. 22 at 3300 (25) cm.$^{-1}$.

Methyl esters under the same conditions of measurement [1] show only the CH_3 symmetrical deformation at [1439 ± 3 cm.$^{-1}$ (110 ± 15)]; however, a weak shoulder on this band is shown [10] for methyl acetate at 1456 cm.$^{-1}$ due to the asymmetrical vibration. The changed environment of the methoxyl group in the ethers thus weakens the intensity of the symmetrical deformation and strengthens that of the asymmetrical deformation; the intensity of the symmetrical CH_3 bending frequency for the methyl ethers is highest for the heterocyclic compounds in which the heterocyclic rings have some of the electron-accepting ability of the carbonyl group.

Ethyl esters show CH_2 scissor [1465 ± 3 cm.$^{-1}$ (35 ± 10)] and wagging modes

[10] Nolin and Jones, *Canad. J. Chem.*, 1956, **34**, 1382.

TABLE 2. *Ethoxy-compounds.*

		1		2		3		4		5	
		CH_2 scissor		CH_3 bending asym.		CH_3 bending sym.		COC asym. stretch			
No.	Ring	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A
1	Ph	1478	95	1445	25	1389	35	1300 1289	45 45	1239	220
2	C_6H_4·NH_2-*m*	1476	75	1444 *	25	1390	40	(—)		1282	70
3	C_6H_4·OEt-*m*	1472	*130*	1447	*70*	1390	*105*	1330	*50*	1282 1260	*120* *120*
4	C_6H_4·Me-*m*	1476	60	1443	35	1390	85	1286	70	1253	120
5	C_6H_4·NO_2-*m*	1471	100	1442	35	1395	80	1282	140	1242	140
6	C_6H_4·NH_2-*p*	1480	85	1443	20	1393	45	1324 1292	15 35	(1230	260)
7	C_6H_4·Me-*p*	1480	35	1442	20	1390	45	1287	40	($CHCl_3$)	
8	C_6H_4·NO_2-*p*	1476	75	1444	25	1395	55	1298	155	1259	390
9	4P	1475	80	1445	20	1395	40	1360 *	25	1285 1255	250 110
10	3P	1472	70	(—)		1390	35	1278 *	105	1258	110
11	2P	1480 ‡	140	(—)		1385	70	1311	160	1286 1247	310 125
12	4PO	1476 ‡	220	1448 †	50	1398	70	—		1292	210
13	4PO(3Me)	(—)		1445 *	90	1393	110	1300 *	80	1281	320
14	3PO	1473	115	(—)		1397	65	—		1308	210
15	2PO	1475 ‡	125	(—)		1398	65	—		1313 1274	310 190

		6		7		8		9	
		CH_2 rock out-of-plane?		CH_2 rock in-plane?		COC sym stretch		C_2H_5 CC stretch	
No.	Ring	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A
1	Ph	1114	55	1089 *	25	1045	135	919	30
2	C_6H_4·NH_2-*m*	1112	50	1090	20	1043	110	972	30
3	C_6H_4·OEt-*m*	1112	*120*	1086	*40*	1044	*175*	984	*25*
4	C_6H_4·Me-*m*	1113	50	1090	20	1045	85	947 * 919	30 70
5	C_6H_4·NO_2-*m*	1111	60	1094 †	75	1042	145	956	40
6	C_6H_4·NH_2-*p*	1114	60	1087	25	1046	115	920	30
7	C_6H_4·Me-*p*	1115	60	1090	20	1045	95	918	50
8	C_6H_4·NO_2-*p*	(—)		1088 *	30	1039	175	920	50
9	4P	1110	45	1088	25	1039 1010 *	190 35	922	50
10	3P	1112	60	1090 *	25	1050 1032	90 50	915	20
11	2P	1115	30	1091	35	1045 † 1030	180 95	921 903	45 15
12	4PO	1114	70	1088	20	1039	230	925	105
13	4PO(3Me)	1108	55	1086	30	1039	240	916	150
14	3PO	1113	60	1092	40	1043	135	915	25
15	2PO	1120 †	195	1090	35	1034	135	928 909	50 35

For symbols, etc., see footnotes to Table 1. Unexplained bands ($\varepsilon_A \geqslant 15$) were shown for compound No. 9 at 1700 (30) and 828 * (40) cm.$^{-1}$; for No. 12 at 1555 (15) cm.$^{-1}$; and for No. 15 at 3370 (135) cm.$^{-1}$.

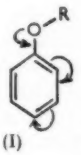
A band for No. 11 at 1266 ‡ (140) cm.$^{-1}$ is probably a nuclear band (cf. Katritzky and Hands, *J.*, 1958, 2202).

[1370 ± 2 cm.$^{-1}$ (100 ± 10)] and CH_3 asymmetric [1446 ± 1 (30 ± 5)] and symmetric bending modes [1391·5 ± 2 cm.$^{-1}$ (30 ± 5)].[1] The CH_2 modes should, because of proximity, show the biggest difference between ester and ether; the wagging mode apparently disappears,* and the scissor mode is shifted and enhanced in intensity. The CH_3 asymmetrical deformation mode is little altered; the symmetrical CH_3 deformation mode is somewhat intensified.

* Possibly the wagging frequency is shifted upwards and contributes to the apparent intensification of the CH_3 symmetrical bending modes.

We are thus able to make a more complete assignment of the bands in this region than previous workers who found [9] absorption at 1471—1453 cm.$^{-1}$ (s) and 1361—1328 cm.$^{-1}$ (s) for methoxy-compounds (assigned respectively to the asymmetrical and symmetrical CH bending modes) and at 1473—1462 and 1389—1387 cm.$^{-1}$ (intensity not indicated) for the ethoxy-compounds (assigned to the asymmetrical and symmetrical methyl and methylene modes [9]). It has also been reported by Jones *et al.*[5] that methoxyl and methyleneoxy (·O·CH_2·) groups do not show characteristic CH deformation frequencies in the 1500—1350 cm.$^{-1}$ region.

The 1350—1240 *cm.*$^{-1}$ *Region.*—For ROR', when R = R' the OR and the OR' stretching modes are coupled, forming an asymmetric and a symmetric mode. If R and R' are appreciably different (*e.g.*, aromatic and aliphatic), coupling is less important, and one mode is principally the OR and the other the OR' stretching frequency. The strong band for the methyl and ethyl ethers (Tables 1 and 2, col. 5) at 1313 to < 1240 cm.$^{-1}$ is principally the ring-oxygen stretching frequency because this has some double-bond character and will therefore absorb at higher frequencies than the alkyl-oxygen mode; the regularities discussed below confirm this assignment. Absorption is similar for corresponding methoxy- and ethoxy-compounds; for the latter the position is −2 to +7 [3 ± 3] cm.$^{-1}$ lower than, and the intensity is 0·6 to 1·3 [0·9 ± 0·2] times greater than, that of the former. The following discussion includes both the methoxy- and ethoxy-compounds.


(I)

The frequency should be higher the greater the electron-withdrawing power of the ring, for this increases mesomerism of type (I) and thus the double-bond character of the oxygen-ring linkage. As expected, all the heterocyclic ethers absorb at higher frequencies than anisole and phenetole and in the order (series 1) of the electron-withdrawing ability of

Ph	< 3P	< 4P ~ 2P	< 4PO	< 3PO ~ 2PO ~ 4PBCl$_3$	....Series 1 *
0	19	44—48	48—52	64—74	cm.$^{-1}$

the ring in various positions, an order which is in agreement with chemical [11] and dipole-moment [12] evidence, with the positions of the ring-nitrogen stretching band for amines,[13] and with the intensity variation of ring nuclear bands.[3] The effect of *para*-substituents in the benzene ring is also as expected (series 2). However, *meta*-substituted benzenes are

NH_2, OMe, OH	< Me	< H	< CH:CHX, C:CX	< NO_2	....Series 2
? (obscured by $CHCl_3$)	−2	0	3—8	18—20	cm.$^{-1}$

anomalous; the position is higher than expected (series 3) for compounds with electron-

H	< NO_2	< Me	< OMe,† OEt,† OH, NH_2	....Series 3
0	2—3	14—16	28—44	cm.$^{-1}$

donor substituents, possibly because of coupling with a nuclear band.

The intensity is (70—150) [(115 ± 30)] for the anisoles and phenetoles with a *meta*-substituent other than a nitro-group; in these phenetoles and in all the other compounds, the intensity is (110—490) [(260 ± 65)]. Frequently a subsidiary to the main aryl-oxygen bond-stretching band is shown at somewhat higher frequencies (Tables 1 and 2, col. 4).

Absorption at 1271—1242 cm.$^{-1}$,[9] at 1270—1230 and up to 1300 cm.$^{-1}$ for *meta*-substituted compounds,[6] and at 1270—1150 cm.$^{-1}$ had previously [7] been assigned to the aryl-oxygen stretching mode.

* In this and the following paper, substituted pyridine, pyridine 1-oxide, and pyridine–boron trichloride nuclei are represented by P, PO, and PBCl$_3$, respectively, together with a numeral to indicate the position of the substituent.

† The band is split in these compounds; average intensities and frequencies are taken.

[11] Katritzky, *Quart. Rev.*, 1956, **10**, 395.
[12] Katritzky, Randall, and Sutton, *J.*, 1957, 1769; Bax, Katritzky, and Sutton, *J.*, 1958, 1254.
[13] Katritzky and R. A. Jones, following paper.

The 1200—1050 *cm.*$^{-1}$ *Region* (Table 2, cols. 6 and 7).—The ethoxy-compounds show bands at 1115—1108 cm.$^{-1}$ (30—70) [1113 ± 2 cm.$^{-1}$ (55 ± 10)] (except in No. 15 where the band is displaced to 1120 cm.$^{-1}$ by overlap) and at 1092—1086 cm.$^{-1}$ (20—40) [1089 ± 2 cm.$^{-1}$ (25 ± 5)] which are probably due to a mode of the ethyl group since no corresponding absorption was found for the methoxy-compounds. Possible assignments are methyl in- and out-of-plane rocking modes.[14] Ethyl esters show a band corresponding to the second but not to the first mode.[1] Briggs *et al.*[9] reported absorption bands at 1122—1117 and 1156 cm.$^{-1}$ for ethoxy-compounds and at 1192—1175 and 1148—1079 cm.$^{-1}$ for methoxy-compounds; in the last three cases this was probably due to aromatic CH in-plane vibrations which are sometimes greatly intensified by alkoxyl groups.[2b,15]

The 1050—1000 *cm.*$^{-1}$ *Region* (Table 1, col. 6; Table 2, col. 8).—Bands shown for the ethoxy-compounds at 1050—1034 [1043 ± 4] cm.$^{-1}$ and by the methoxy-compounds at 1048—1013 [1034 ± 8] cm.$^{-1}$ are assigned to a mode involving mainly alkyl–oxygen bond stretching, in agreement with Briggs *et al.*[9] who found these bands at 1048—1024 and 1042—1000 cm.$^{-1}$ for ethoxy- and methoxy-compounds, respectively, and others [6,7] who quote ranges of 1070—1000 cm.$^{-1}$ and 1120—1030 cm.$^{-1}$. The band is split for *m*-dimethoxybenzene, and average values of position and intensity have been used in the following treatment; when splitting occurs for other compounds, the position and intensity of the strongest component have been taken.

Absorption for corresponding pairs is 0—12 [7 ± 4] cm.$^{-1}$ higher and 0·8—1·3 [1·0 ± 0·15] times as intense for the ethoxy- as for the methoxy-compounds. Intensities

3P <	4PBCl$_3$ <	3PO ~	Ph <	4P <	4PO,4PO(3Me)....Series 4
90	100	115—135	130—135	190—205	230—285

are (80—170) [(115 ± 20)] for all the benzenoid compounds except those with a *p*-nitro-substituent, for which they are (175—190). The relative intensities for the heterocyclic compounds, anisole, and phenetole (series 4) do not bear any obvious relation to the nature of the ring.

The 1000—900 *cm.*$^{-1}$ *Region* (Table 2, col. 9).—A band occurs at 928—915 [920 ± 4] cm.$^{-1}$ for all the ethoxy-compounds except *m*-amino-, *m*-ethoxy-, and *m*-nitro-phenetole, for which the position is 984—956 cm.$^{-1}$. The intensity is (20—70) [(40 ± 15)] except for the 4PO and the 4PO(3Me) compound, where it is (105—150). This band is tentatively assigned to the CC stretching mode of the ethyl group.[14]

Nuclear Bands.—The compounds also show bands due to vibrations of the nuclei; these have been published [2] for 2-, 3-, and 4-monosubstituted pyridines, for 2-, 3-, and 4-monosubstituted pyridine 1-oxides, and for monosubstituted benzenes. Very few bands ($\varepsilon_A \geqslant 15$) were found which could not be assigned to the alkoxyl group, nucleus, or other substituent; the exceptions are shown in footnotes to Tables 1 and 2.

Experimental.—References to the methods for the preparation of the compounds are given elsewhere.[1-3] The spectra were measured on the Oxford Perkin-Elmer 21 spectrophotometer with a sodium chloride prism, slit programme 4, and the settings previously given.[1] ε_A values were calculated as in ref. 2(*b*).

We thank Dr. N. Sheppard for reading this and the following paper in manuscript; part of this work was carried out during the tenure (by A. R. K.) of an I.C.I. Fellowship.

The Dyson Perrins Laboratory, Oxford.
The University Chemical Laboratory, Cambridge. [*Received, December 11th,* 1958.]

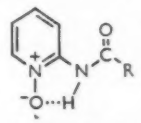
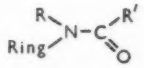
[14] Cf. Sheppard and Simpson *Quart. Rev.*, 1953, **7**, 19.

416. *Infrared Absorption of Substituents in Aromatic Systems. Part II.*[1] *Acylamino-compounds.*

By A. R. Katritzky and R. A. Jones.

The absorption caused by the groups ·NH·COMe, ·NH·CO·, ·NMe·COMe, and ·NMe·CO· for a total of twenty-four acetamido-, *N*-methylacetamido-, benzamido-, and *N*-methylbenzamido-compounds is recorded. Tentative assignments are made for most of the characteristic bands, and the dependence of their positions and intensities on the structure of the compounds is discussed. More than 98% of the bands ($\varepsilon_A \geqslant 15$) for these compounds were correlated with the rings or substituent groups.

The infrared spectra of monosubstituted amides have been extensively investigated because of the importance of the amide linkage in polypeptides and proteins, but the interest has been mainly in the NH and C:O stretching bands ("amide I" and the "amide II" bands[2,3]). Of the amido-benzenoid or -heteroaromatic compounds, acetanilide has been studied in detail,[4] and series of substituted[5] and fatty acid[6] anilides and some acetamidopyrimidines[7] have been investigated. The most comprehensive work on the assignment of skeletal frequencies is by Miyazawa *et al.*[8]

(I)  (II) 

While investigating the infrared absorption of heteroaromatic rings[9–15] and the tautomerism of acylaminopyridines and their oxides,[16] we studied a series of acetamido- and benzamido-compounds and their *N*-methyl derivatives. Almost all the bands were characteristic of either the rings or the substituents; those characteristic of the groups ·NH·CO·, ·NMe·CO·, ·NH·COMe, and ·NMe·COMe are recorded in Table 1 with cross-references to the benzenoid and heteroaromatic bands (col. 19). When sufficiently soluble, the compounds were measured in 0·2M-chloroform solutions in a 0·117 mm. cell;[17] otherwise 0·02M-solutions (1 mm. cell) or, in one case, a Nujol mull were used.

The NH *Stretching Band.*—The non-bonded NH stretching frequency (possibly the *trans*-peak[18]) is shown by the compounds X·NH·COMe and X·NH·COPh in solution at 3440—3410 [3420 ± 10]* cm.$^{-1}$ (except for the 2-substituted pyridine 1-oxides); the intensities are (30—45)* in 0·2M- and (45—65) in 0·02M-solutions and are affected more by

* Parentheses signify apparent molecular extinction coefficients, and square brackets indicate arithmetical means and standard deviations; see preceding paper.

[1] Part I, Katritzky and Coats, preceding paper.
[2] Bellamy, "The Infrared Spectra of Complex Molecules," 2nd edn., Methuen, London, 1958, pp. 203—223.
[3] R. N. Jones and Sandorfy in Weissburger, "Technique of Organic Chemistry. Vol. IX. Chemical Applications of Spectroscopy," Interscience Publ. Inc., London, 1956, pp. 509—531.
[4] Abbott and Elliot, *Proc. Roy. Soc.*, 1956, *A*, **234**, 247.
[5] Richards and Thompson, *J.*, 1947, 1248.
[6] Dijkstra and Jonge, *Rec. Trav. chim.*, 1956, **75**, 1173.
[7] Brownlie, *J.*, 1950, 3062.
[8] Miyazawa, *J. Chem. Soc. Japan*, 1956, **77**, 171; Miyazawa, Shimanouchi, and Mizushima, *J. Chem. Phys.*, 1956, **24**, 408; *Spectrochim. Acta*, 1957, **10**, 217.
[9] Katritzky and Gardner, *J.*, 1958, 2198.
[10] Katritzky, R. A. Jones, and Hands, *ibid.*, p. 3165.
[11] Katritzky and Hands, *J.*, 1958, 2202.
[12] Katritzky and Gardner, *ibid.*, p. 2192.
[13] Katritzky, Beard, and Coats, unpublished work.
[14] Katritzky and Hands, *ibid.*, p. 2195.
[15] Katritzky and Lagowski, *ibid.*, p. 4155.
[16] R. A. Jones and Katritzky, (*a*) *J.*, 1959, 1317; (*b*) unpublished work.
[17] Katritzky, Monro, Beard, Dearnaley, and Earl, *J.*, 1958, 2182.

TABLE 1.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
	νNH	νNH H-bonded	νCO	Amide II	N–Me Me asym bend	?	N–Me Me sym bend	COMe Me sym bend	C–N–C (O)	Two CN stretching modes		N–Me Me rock	?	N–Me Me rock	N–Me ?	COMe Me rock	N–Me N–C stretch	Unassigned bands	Ref. to ring bands
No. Ring	cm.$^{-1}$ ε_A	cm.$^{-1}$ ε_A	cm.$^{-1}$ ε_A	cm.$^{-1}$ ε_A	cm.$^{-1}$ ε_A	cm.$^{-1}$ ε_A	cm.$^{-1}$ ε_A	cm.$^{-1}$ ε_A	cm.$^{-1}$ ε_A	cm.$^{-1}$ ε_A	cm.$^{-1}$ ε_A	cm.$^{-1}$ ε_A	cm.$^{-1}$ ε_A	cm.$^{-1}$ ε_A	cm.$^{-1}$ ε_A	cm.$^{-1}$ ε_A	cm.$^{-1}$ ε_A	cm.$^{-1}$ ε_A	
Compounds X·NH·COMe																			
1 Ph	3420 45	3310 30	1688	330	{1548* 95 1524 300	A	—	A	1373 93	1314 175	1297* 60	1248 135	A	—	A	A	(—)	A	1488* 70	15
2 4P[a]	3440 65	—	1711	280	(CHCl$_3$)	A	1405 50	A	1368 85	1328 150	(1277 90)	(CHCl$_3$)	A	—	A	A	(—)	A	—	9
3 3P	3425 30	3260* 35	1690	250	{1538* 170 1513 200	A	1411 155	A	1369 90	1326 95	1282 120	(CHCl$_3$)	A	—	A	A	998 20	A	—	10
4 2P	3410 40	3180* 25	1694	255	{1527* 120 1508 290	A	1400* 35	A	1367 80	1300 350	(CHCl$_3$)	(CHCl$_3$)	A	(—)	A	A	961 15	A	1035* 15	11
b 4PO[b]	*c*	*c*	1700	s	1500* s	A	—	A	1363 s	1320 s	1263 w	1245* w	A	1100* w	A	A	958 w	A	918 w	16*b*
6 3PO[d]	3410 w	—	1707	s	(CHCl$_3$)	A	1405 w	A	1368 w	1296 m	(CHCl$_3$)	(CHCl$_3$)	A	—	A	A	973 w	A	—	13
7 2PO	—	3280 75	1710	330	1505 400	A	1400* 95	A	1368 90	1313 110	1270 160	(—)	A	—	A	A	{997 35 955 30	A	843* 20	14
Compounds X·NMe·COMe																			
8 Ph	A	A	1653	340	A	1426 80	—)	1384 200	1356 75	1330 20	1297 70	1246* 25	1138 60	1086 40	1035* 15	—	975 35	—	—	15
9 4P	A	A	1665	310	A	{1435* {(—) 45	(—)	1377 220	1332 105	1320 60	1295 100	(CHCl$_3$)	1138 50	1086 15	1030 15	—	975 30	925 10	—	16*a*
10 3P	A	A	1658	340	A	1420† 140	—	1382 170	1354 85	1325 40	1299 90	(CHCl$_3$)	1138 60	1087 30	(—)	—	973 30	—	—	10
11 2P	A	A	1660	320	A	1424* 150	—	1378 215	1349 125	1315 55	1299 70	1285* 60	1140† 90	1090† 25	1032* 25	1005* 30	978 30	—	—	16*a*
12 4PO	A	A	1668	320	A	1423 65	—	1374 170	1343 90	1308 50	1288* 60	(—)	1141 100	1092 20	(—)	1000 50	975 45	921 20	—	12
13 2PO	A	A	1682	420	A	1425* 180		1375 205	1351 160	1311 155	(—)	(—)	1143 110	1080 55	1025* 10	997 10	972 35	925 20	—	16*b*
Compounds X·NH·COPh																			
14 Ph[a]	3420 60	—	1679	310	(CHCl$_3$)	A	(CHCl$_3$)	A	A	1313 190	(CHCl$_3$)	(CHCl$_3$)	A	1096 40	A	A	A	A	1035 30	15
15 4P[a]	3430 45	—	1696	170	(CHCl$_3$)	A	1409 40	A	A	1330 175	(CHCl$_3$)	(CHCl$_3$)	A	{1100* 40 1090 50	A	A	A	A	—	9, 15
16 3P	3420 45	3300* 30	1679	210	1518 220	A	1413* 120	A	A	1329 125	1280 135	(CHCl$_3$)	A	(—)	A	A	A	A	836 15	10, 15
17 2P	3430 55	—	1682	290	{1515 310 1493 220	A	1402* 35	A	A	1306 450	1253* 65	(CHCl$_3$)	A	(—)	A	A	A	A	—	11, 15
18 2PO	—	3280 45	1693	290	1505 460	A	(—)	A	A	{1322* 70 1310 95	{1300* 80 1274 280	(—)	A	1085 35	A	A	A	A	—	14, 15
Compounds X·NMe·COPh																			
19 Ph	A	A	1641	360	A	1423 100	—	1372 280	A	1330 30	1303 115	1280 70	1108 90	(—)	1053 10	{1025 60 1012 15	A	919 10	—	15
20 4P	A	A	1652	280	A	—)	—	1356 300	A	1326 115	1304 200	(CHCl$_3$)	1106 75	(—)	1043 90	{1020* 35 1009 120	A	920 10	—	16*a*
21 3P	A	A	1648	350	A	1423† 120	—	1362 240	A	1326 55	1304 140	(CHCl$_3$)	1111 85	—	1050* 15	1005 30	A	918 10	—	10, 15
22 2P	A	A	1650	360	A	1416 125	—	1359 315	A	1320 90	1300 80	1288 140	1117 100	(—)	(—)	{1020* 30 1012 60	A	920 10	1174 30	11, 15
23 4PO	A	A	1660	350	A	{1436* 55 1423 60	—	1353 260	A	1319 90	1296 145	(—)	1109 90	(—)	(—)	{1021 70 1008 155	A	922 15	{1555 15 3335 20	12, 15
24 2PO	A	A	1665	370	A	1417 130	—	1355 260	A	1330 230	1295* 240	(—)	1098 95	(—)	(—)	1009 70	A	920 5	—	14, 15

* Shoulder. † Absorption considered to be the superimposition of two peaks. — Absence of absorption. (—) Band masked by stronger absorption. (CHCl$_3$) Band masked by solvent. A, Band neither expected nor found.

Ph phenyl, P substituted pyridine, PO substituted pyridine 1-oxide; the position of the substituent is indicated by a numeral.

a, 0·02M-solution in 0·1 mm. cell. *b*, Nujol mull. *c*, Broad absorption. *d*, Saturated solution (<0·02M) in 0·1 mm. cell.

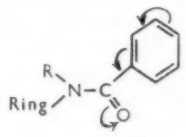
the concentration than by the nature of the ring. Thompson and his co-workers [18] found that *meta*- and *para*-substituents have little effect on the position, half band-width, and integrated intensity (and therefore also ϵ_A) of this band for acetanilide; concentration does affect the intensity, and at infinite dilution acetanilide absorbs at 3436 cm.$^{-1}$ (125) (lithium fluoride prism).

The compounds measured at 0·2M-concentration usually show absorption at *ca.* 3300 cm.$^{-1}$ due to the hydrogen-bonded NH groups.[2] In the 2-substituted pyridine 1-oxides intramolecular bonding (cf. I) lowers the frequency to 3280 cm.$^{-1}$.

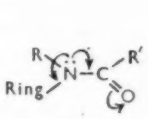
The C:O *Stretching Band* (Table 1, col. 3).—This, the amide I band, occurs at 1711—1641 cm.$^{-1}$; the influence of R, R′, and the ring (cf. II) can be distinguished.

(i) Changing R′ from methyl to phenyl (cf. II) increases the conjugation of the carbonyl group (III) and lowers the frequency by 8—17 [12 ± 3] cm.$^{-1}$.

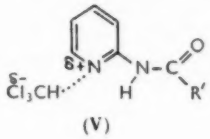
(ii) Changing R from hydrogen to methyl also increases considerably the conjugation of the carbonyl group, both because of the favourable inductive effect of the methyl group and, probably more importantly, by causing partial steric inhibition of mesomerism between the nitrogen atom and the ring for which there is independent evidence from basicities and ultraviolet spectra.[16] The frequency is lowered by 25—46 [35 ± 6] cm.$^{-1}$.



(III)



(IV)



(V)

(iii) Changing the ring from phenyl to pyridine or pyridine 1-oxide always raises the frequency (Table 2), indicating that the heterocyclic rings are all more strongly electron-accepting than phenyl and conjugate more tightly with the amide-nitrogen atom, thus causing this atom to conjugate less with the carbonyl group (cf. IV). The increment is larger for the 4- than for the 3-substituted pyridines, as expected from the relative electron-withdrawing abilities of these rings.[1,19] The large increments found for all the pyridine 1-oxides agree with the known ability of this ring to withdraw electrons strongly at each nuclear position.[1,19,20] The increments are smaller than expected in the 2-pyridyl series, possibly owing to steric inhibition of hydrogen bonding of the pyridine nitrogen atom to the solvent [11] (cf. V).

TABLE 2. *Carbonyl stretching bands. Increments in wavenumbers over that for the corresponding benzenoid compound.*

	4P	3P	2P	4PO	3PO	2PO
NH·COMe	23	2	6	(12) [a]	19	22
NH·COPh	17	0	3	—	—	14
NMe·COMe	12	5	7	15	—	29
NMe·COPh	11	7	9	19	—	24

[a] Difference obtained by using paraffin-paste spectrum. See also footnotes to Table 1.

The intensities are (170—330) [(270 ± 55)] for ·NH·COPh and ·NH·COMe compounds and (280—420) [(345 ± 40)] for ·NMe·COPh and ·NMe·COMe compounds.

The frequency range of this band agrees with previous work.[2] Similar raising of the frequency as the ring becomes increasingly electron-accepting has been noted for *meta*- and *para*-substituted acetanilides [5] and acetyl-azoles.[21]

[18] Russell and Thompson, *J.*, 1955, 483; *Spectrochim. Acta*, 1956, **8**, 138; Moccia and Thompson, *ibid.*, 1957, **10**, 240.
[19] Katritzky, *J.*, 1958, 4162.
[20] Katritzky, *Quart. Rev.*, 1956, **10**, 395.
[21] Otting, *Chem. Ber.*, 1956, **89**, 1940.

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The Amide II *Band* (Table 1, col. 4).—For the X·NH·COMe and X·NH·COPh compounds the band is found at 1524—1505 cm.$^{-1}$ (200—460) [1513 ± 7 cm.$^{-1}$ (310 ± 100)], often with a shoulder or subsidiary band. The region is obscured by chloroform when measured in a 0·1 mm. cell. This band usually occurs at 1580—1475 cm.$^{-1}$ and is due to the NH in-plane deformation frequency coupled with the N–C stretching frequency of the ·NH·CO· group.[2,3,8,22]

The 1450—1400 *cm.*$^{-1}$ *Region.*—The X·NMe·COMe and X·NMe·COPh compounds show a band at 1426—1416 cm.$^{-1}$ (60—130) [1422 ± 4 cm.$^{-1}$ (90 ± 25)] (Table 1, col. 5). This is probably the asymmetric N–CH_3 CH-bending frequency which occurs at 1465—1442 cm.$^{-1}$ for compounds of type R·CO·NHMe.[8]

Some of the X·NH·COMe and X·NH·COPh compounds show a shoulder or band of unknown origin at 1413—1400 cm.$^{-1}$ (40—155) (col. 6).

The 1400—1340 *cm.*$^{-1}$ *Region.*—Absorption (col. 7) by the X·NMe·COMe compounds at 1384—1374 cm.$^{-1}$ (170—220) [1378 ± 4 cm.$^{-1}$ (195 ± 20)] and by the X·NMe·COPh compounds at 1372—1353 cm.$^{-1}$ (240—310) [1360 ± 7 cm.$^{-1}$ (275 ± 30)] is probably the CH symmetrical bending frequency previously found [8] at 1414—1401 cm.$^{-1}$ for R·CO·NHMe compounds.

The symmetrical CH bending of the acetyl-methyl group causes absorption (col. 8) at 1373—1363 cm.$^{-1}$ (80—95) [1368 ± 3 cm.$^{-1}$ (85 ± 5)] for the X·NH·COMe compounds and at 1356—1343 cm.$^{-1}$ (75—160) [1351 ± 4 cm.$^{-1}$ (105 ± 30)] for the X·NMe·COMe compounds. The ring appears to play a constant rôle in determining the position of the band, for the band is 15—20 [17 ± 2] cm.$^{-1}$ lower for the ·NMe·COMe than for the corresponding ·NH·COMe compound. For comparison, compounds X·COMe [17] absorb at [1359 ± 1·5 cm.$^{-1}$ (135 ± 20)], compounds R·O·COMe [23,24] at *ca.* 1375—1365 cm.$^{-1}$, and compounds R·NH·COMe [8] at 1375—1366 cm.$^{-1}$.

The 1340—1240 *cm.*$^{-1}$ *Region.*—Stretching frequencies of the two C–N partial double bonds (cf. IV) are expected in this region. Belonging to the same symmetry class, they will combine to give symmetric and asymmetric modes. With the NH-compounds, the NH in-plane deformation should also intereact with these modes.

Two or three bands are shown (Table 1, cols. 9—11). As expected from the above discussion, the absorption depends little on whether R′ is Me or Ph (II), more on the nature of the ring, and most on whether R is Me or H.

(i) The first band (col. 9) is at 1330—1300 [1319 ± 10] cm.$^{-1}$; there is no simple relation between the precise position and the structure. The intensities vary for the X·NMe·COMe and X·NMe·COPh compounds (20—230), but the band for X·NMe·COPh is always 1·4—1·9 [1·60 ± 0·2] times as intense as that for the corresponding X·NMe·COMe compounds; for these compounds the intensities increase as the rings become more electron-accepting:

$$\text{Ph} < 3\text{P} < 2\text{P} \sim 4\text{P} \sim 4\text{PO} < 2\text{PO}$$

For the compounds X·NH·COMe and X·NH·COPh the intensities vary (95—450); for corresponding compounds, replacing NH by NMe increases the intensity 0·9—1·3 [1·15 ± 0·2] times; there is no simple relation between intensity and the ring type.

(ii) For the X·NMe·COMe and X·NMe·COPh compounds the second band (col. 10) is at 1304—1295 cm.$^{-1}$ (70—200) [1299 ± 3 cm.$^{-1}$ (110 ± 45)] except for No. 24. This band appears to occur at *ca.* 1280—1260 cm.$^{-1}$ for the X·NH·COMe and X·NH·COPh compounds, but this region is often obscured by solvent (1 mm. cell).

(iii) A third band sometimes appears (col. 11) on the edge of the region obscured by solvent absorption, *i.e.*, below 1240 cm.$^{-1}$ (0·1 mm. cell).

The 1200—1100 *cm.*$^{-1}$ *Region* (Table 1, col. 12).—The X·NMe·COMe compounds show a band at 1143—1138 cm.$^{-1}$ (50—110) [1140 ± 2 cm.$^{-1}$ (75 ± 20)], and the X·NMe·COPh

[22] Frazer and Rice, *Nature*, 1952, **170**, 490.
[23] Francis, *J. Chem. Phys.*, 1951, **19**, 942.
[24] R. N. Jones and Cole, *J. Amer. Chem. Soc.*, 1952, **74**, 5648.

compounds one at 1117—1098 cm.$^{-1}$ (75—100) [1108 ± 6 cm.$^{-1}$ (90 ± 8)]; these are probably *N*-methyl rocking frequencies, occurring [8] at 1179—1149 cm.$^{-1}$ for R·CO·NHMe compounds.

The 1100—800 *cm.*$^{-1}$ *Region.*—A band of unknown origin is found for the compounds X·NMe·COMe and X·NH·COPh at 1096—1080 cm.$^{-1}$ (15—55) [1088 ± 5 cm.$^{-1}$ (35 ± 10)] (col. 13).

The X·NMe·COPh compounds show a band at 1053—1030 cm.$^{-1}$ (10—20) (col. 14) and a doublet at 1025—1021 and 1012—1005 cm.$^{-1}$ (30—155) (col. 15); the analogous absorption for the X·NMe·COMe compounds, which is weaker or absent, occurs at *ca.* 1030 and 1000 cm.$^{-1}$. The compounds X·NMe·COMe and X·NMe·COPh show a band at 925—918 cm.$^{-1}$ (5—20) [921 ± 2 cm.$^{-1}$ (10 ± 5)] (col. 17). Two of these bands are probably due to C–N stretching and Me rocking modes of the N–CH_3 group; a possible assignment is indicated in Table 1.

A band, probably an acetyl-methyl rocking mode (col. 16), occurs at 978—972 cm.$^{-1}$ (30—50) [975 ± 2 cm.$^{-1}$ (40 ± 8)] for the X·NMe·COMe compounds and at 998—958 cm.$^{-1}$ (15—35) [978 ± 19 cm.$^{-1}$ (25 ± 10)] for the X·NH·COMe series. A band or oublet at 1041—987 cm.$^{-1}$ for CH_3CO·NHR compounds has been assigned [8] to a Me rocking mode, and methyl ketones show a band at [959 ± 5 cm.$^{-1}$ (35 ± 15)].[17]

Other Bands.—Nearly all the remaining bands ($\varepsilon_A \geqslant 15$) for these compounds could be assigned to the heterocyclic and/or benzenoid rings; most have been published (see refs. in col. 19). Bands which could not be correlated in this way are given in col. 18; they form 2% of the total.

Experimental.—See Part I [1] for details.

Dyson Perrins Laboratory, Oxford.
University Chemical Laboratory, Cambridge. [*Received, December 11th,* 1958.]

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417. *The Mechanisms of Inhibition and Retardation in Radical Polymerizations. Part V.* The Effects of Picric Acid and* m*-Dinitrobenzene on the Sensitized Polymerization of Styrene.*

By J. C. Bevington and N. A. Ghanem.

The effects of picric acid and *m*-dinitrobenzene on the sensitized radical polymerization of styrene have been examined The former acts as a rather inefficient inhibitor and is converted into a substance which is a retarder for the subsequent polymerization; *m*-dinitrobenzene is a retarder. ^{14}C-labelled specimens of the nitro-compounds have been used to determine the amounts incorporated in the polymers. The effects of the nitro-compounds on the average number of initiator fragments in each polymer molecule have been studied by using labelled initiator. Treatment of polymers with trifluoroacetic anhydride reduces the molecular weight and removes combined nitro-compound from the polymer. A reaction scheme is suggested which satisfies the observations.

Many aromatic nitro-compounds act as chain terminators for radical polymerizations but the mechanisms by which they exert their effects are uncertain. It has been suggested [1] that the polymer radical becomes attached directly to the aromatic nucleus of the nitro-compound, but other authors [2] suppose that the attack is on the nitro-group itself. The products of the interaction of 1-cyano-1-methylethyl radicals and various nitro-compounds have recently been identified; [3] this work is of significance in connection with the effects of

* Part IV, Bevington and Ghanem, *J.*, 1958, 2254.

[1] Price and Durham, *J. Amer. Chem. Soc.*, 1943, **65**, 757.
[2] Bartlett, Hammond, and Kwart, *Discuss. Faraday Soc.*, 1947, **2**, 342.
[3] Inamoto and Simamura, *J. Org. Chem.*, 1958, **23**, 408.

nitro-compounds on radical polymerizations. In this paper a study of the effects of picric acid and *m*-dinitrobenzene on the polymerization of styrene is reported; it involved the use of labelled nitro-compounds and labelled azoisobutyronitrile as initiator.

Previous tracer studies of the effects of retarders of various types have given useful information on the natures of the reactions involved.[4] The experimental work has been directed chiefly to determination of the numbers of molecules of retarder and fragments of initiator incorporated on the average in each polymer molecule for reactions carried out under various conditions. In some cases it has been possible to discover the way in which the retarder is linked in the polymer by examining the effects of chemical treatment upon the specific activities of polymers prepared by using labelled reagents.

Experimental

Descriptions have already been published for the various experimental procedures.[4] Standard methods were used for the preparation of [^{14}C]*m*-dinitrobenzene from [^{14}C]benzene. The product was recrystallized from ethanol; its specific activity was about 11 μcuries/g. of carbon. The labelled picric acid was an intermediate in the preparation of [^{14}C]diphenylpicrylhydrazine and the corresponding hydrazyl.[5] It was purified by recrystallization from aqueous ethanol; its specific activity was about 25 μcuries/g. of carbon.

Results.—Separation tests. Blank experiments with labelled contaminants showed that all traces of uncombined picric acid and *m*-dinitrobenzene could be removed from polystyrene by two precipitations of the polymer from benzene, methanol being used as precipitant.

Experiments with picric acid. Polymerizations of styrene in bulk at 60° were initiated by azoisobutyronitrile at a concentration close to 0·300 g./l. The concentration of picric acid ranged from 0 to about 0·1 g./l. Results are summarized in Table 1, and typical conversion–time curves are shown in Fig. 1. Reactions were carried to 5% conversion.

Experiments with [^{14}C]picric acid showed that appreciable quantities were incorporated in the polymer. On use of [^{14}C]picric acid giving a counting rate of 177,000 counts/min., polymers 3 and 4 gave counting rates of 44 and 56 counts/min., respectively. From the counting rates of

Table 1.

Expt. no.	Concn. of initiator (g./l.)	Concn. of picric acid (g./l.)	Time to reach steady rate (hr.)	Steady rate (%/hr.)	Molecular weight of polymer
1	0·300	0	0	1·37	264,000
2	0·297	0·049	7	0·99	169,000
3	0·292	0·050	7	1·06	169,000
4	0·294	0·073	9	0·84	126,000
5	0·303	0·099	11	0·70	114,000

the polymers and the original picric acid and the molecular weights of the polymers, it is calculated that for both polymers just over 0·5 molecule of picric acid was combined on the average in each polymer molecule. Polymer 4 was treated with diethyl ether and its counting rate was reduced to 7 counts/min., showing that a large proportion of the combined picric acid was contained in polymer of comparatively low molecular weight.

Polymers 2 and 5 were prepared by using ^{14}C-initiator and unlabelled picric acid; the average number of initiator fragments per polymer molecule for these polymers was close to 1·5. In polymer 1, prepared in the absence of picric acid, there were 2·0 initiator fragments per polymer molecule. A specimen of polymer 2 was treated with diethyl ether; about 20% of the polymer was soluble in the ether and the counting rate of the insoluble portion was 123 counts/min. compared with 228 counts/min. for the whole polymer.

Polymer 2 was treated with trifluoroacetic anhydride reagent; its average molecular weight fell to 140,000 but there were no significant changes in the total weight of the specimen or its counting rate. Similar treatment of polymer 3, containing labelled picric acid, reduced its counting rate to 12 counts/min., and isotope dilution analysis showed that about 70% of the labelled groups lost from the polymer appeared as picric acid.

[4] Bevington, Ghanem, and Melville, *J.*, 1955, 2822.
[5] Bevington, *J.*, 1956, 1127.

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A solution of [^{14}C]azoisobutyronitrile (17·0 mg.) and picric acid (20·6 mg.) in benzene (3·5 c.c.) was degassed and kept at 60° for 17½ hr. By isotope dilution analysis, it was found that 1·6 mg. of tetramethylsuccinodinitrile and 0·3 mg. of isobutyronitrile were produced; in a similar experiment in the absence of picric acid, the weights of these products were 3·2 mg. and 1·4 mg., respectively.

Experiments with m-*dinitrobenzene.* Polymerizations of styrene at 60° with a fixed concentration of azoisobutyronitrile (close to 0·300 g./l.) and various concentrations of *m*-dinitrobenzene are referred to in Fig. 2 and Table 2; reactions were allowed to proceed to 6% conversion. As indicated in Table 2, some experiments involved ^{14}C-retarder and others ^{14}C-initiator; the results of experiment 1 are included for comparison. The average numbers of

FIG. 1. *Conversion–time plots for the polymerization of styrene at 60° (curves labelled with experiment numbers as in Table 1).*

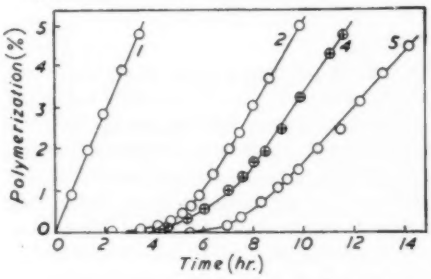
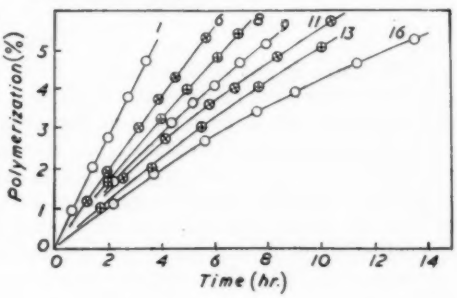


FIG. 2. *Conversion–time plots for polymerization of styrene at 60° (curves labelled with experiment numbers as in Table 2).*



retarder molecules or initiator fragments incorporated in the polymer molecules are shown in Table 2.

TABLE 2.

Expt. no.	Concn. of retarder (g./l.)	Molecular weight of polymer	Counting rate for polymer (counts/min.)	No. of initiator fragments per molecule	No. of retarder molecules per molecule
1	0	264,000	197 [a]	2·00	—
6	0·203	187,000	220 [a]	1·58	—
7	0·251	177,000	16	—	0·5
8	0·319	151,000	288 [a]	1·67	—
9	0·404	126,000	20	—	0·4
10	0·500	111,000	24	—	0·4
11	0·504	114,000	330 [a]	1·44	—
12	0·698	99,000	41	—	0·6
13	0·690	97,000	110 [b]	1·25	—
14 [c]	0·704	94,000	105 [b]	1·15	—
15	0·989	75,000	54	—	0·7

[a] Counts/min. for initiator = 500,000. [b] Counts/min. for initiator = 165,000; counts/min. for retarder = 76,000. [c] Polymerization carried to 3% conversion only.

From the polymerizations involving ^{14}C-initiator, average kinetic chain lengths were calculated, and thence average rates and efficiencies of initiation. In these calculations, the average rates of polymerization over the whole reactions were used. In some cases, appreciable decomposition of the initiator occurred during the reaction and the mean of the initial and final concentrations was used in calculating the efficiencies; for calculation of the final concentration, k_d was taken as $1{\cdot}30 \times 10^{-5}$ sec.$^{-1}$. The results of these calculations are summarized in Table 3.

A solution of azoisobutyronitrile (10·9 mg.) and [^{14}C]*m*-dinitrobenzene (10·2 mg.) in benzene (2·5 c.c.) was degassed and sealed in vacuum. After 16 hr. at 60°, no *m*-nitronitrosobenzene could be detected in the reaction mixture by isotope dilution analysis.

Refluxing polymers 7 and 9 with trifluoroacetic anhydride reagent for 10 and 15 hr. respectively caused the counting rates of the polymers to fall to about 8 counts/min. Isotope dilution

TABLE 3.

Expt. no.	Rate of polym. $\times 10^5$ (mole $l.^{-1}$ $sec.^{-1}$)	Average concn. of initiator (g./l.)	Kinetic chain length	Rate of initn. $\times 10^8$ (mole $l.^{-1}$ $sec.^{-1}$)	Efficiency of initiation (%)
1	3·18	0·29	1270	2·51	54·6
6	2·13	0·26	1136	1·88	45·6
8	1·76	0·26	868	2·03	49·2
11	1·37	0·24	833	1·64	43·1
13	1·11	0·23	750	1·48	40·6
14	1·28	0·27	786	1·63	38·1

analysis for *m*-dinitrobenzene produced during treatment of polymer 9 showed that a small amount was liberated. The counting rates of the materials in the experiments were so low that the analysis was qualitative only.

DISCUSSION

Picric acid is not an ideal inhibitor for the radical polymerization of styrene since polymerization is not suppressed completely; the rate gradually rises to a steady value and the induction period does not end abruptly. The steady rate falls as the initial concentration of picric acid is raised; the effect is too large to be accounted for by the consumption of initiator during the early stages of the reaction. The concentrations of initiator remaining when the steady rates were first attained in experiments 2—5 have been calculated; rates of polymerization corresponding to these concentrations have been calculated by taking experiment 1 as standard and assuming an order of 0·5 with respect to initiator. The rates thus calculated for experiments 2, 3, 4, and 5 are respectively 1·16, 1·15, 1·13, and 1·05%/hr.; these rates are respectively 1·17, 1·08, 1·35, and 1·50 times the observed rates. The discrepancy between observed and calculated rates increases with rising concentration of picric acid, suggesting that during the early stages the picric acid is converted into a retarder, the amount of which increases as the initial concentration of the acid is raised. This conclusion is confirmed by the differences between the molecular weights of the polymers in this series.

The incorporation of picric acid in the polymer disproves certain of the mechanisms suggested for the interaction of polymer radicals and nitro-compounds. The effect of trifluoroacetic anhydride upon the molecular weight of a polymer prepared in the presence of picric acid shows that the polymers contain linkages sensitive to the reagent; it is likely that the picric acid combined in the polymer is not held by carbon–carbon bonds since most of the combined acid can be eliminated from the polymer by treatment with the reagent. Most of the picric acid eliminated from the polymer appears as such, suggesting that the picric acid unit is intact in the polymer.

It is likely that one of the nitro-groups in the molecule of picric acid is involved in the first stages of the reaction, and that the unused nitro-groups are concerned in the subsequent retardation process. No significance can be attached to the relative numbers of initiator fragments and picric acid molecules combined in the polymers, since the picric acid acts in two distinct ways during the course of the polymerization. The results of the experiments involving diethyl ether show that the polymers contain much material of fairly low molecular weight, so that some fractionation may well occur during recovery of the polymers.

m-Dinitrobenzene retards the polymerization of styrene but it also interferes in the initiation step since its presence reduces the efficiency of initiation. The continuous decrease in rate during the course of a retarded polymerization (see Fig. 2) can be accounted for by the consumption of initiator; at the end of experiment 13, for example, the concentration of initiator had fallen to about 55% of its original value. Part, at least, of the *m*-dinitrobenzene included in the polymer is not held by carbon–carbon bonds since much of it can be removed by treatment with trifluoroacetic anhydride.

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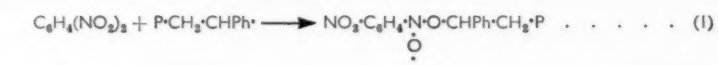
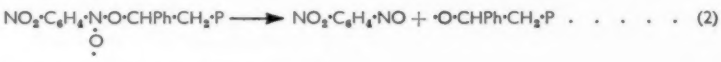
The results of Inamoto and Simamura [3] indicate that the first stage in the interaction of a polymer radical with *m*-dinitrobenzene is likely to be



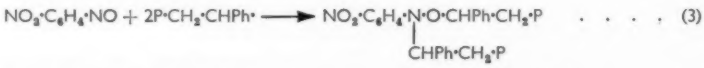
(1)

where P represents a polystyrene chain with a terminal initiator fragment. According to the suggestion of these authors, the next stage is the formation of the nitroso-compound

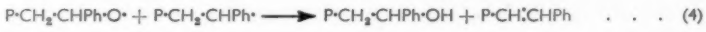


(2)

The products of this reaction might react as follows:



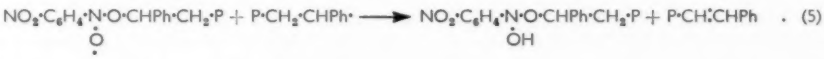
(3)



(4)

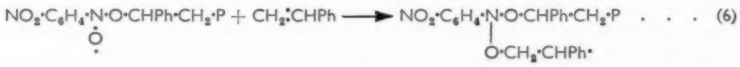
If these processes were the sole terminating reactions, the average numbers of initiator fragments and retarder molecules per polymer molecule would be **1·33** and **0·33**, respectively. If reaction (3) did not occur, the number of initiator fragments would be **1·00**, but no retarder would be incorporated in the polymer, contrary to the observations made in this work; further, no *m*-nitronitrosobenzene could be detected in the products of the interaction of 1-cyano-1-methylethyl radicals with *m*-dinitrobenzene. If mutual termination occurred at the same time as the termination involving the nitro-compound, the average number of combined initiator fragments would be greater than **1·33** and that of combined retarder molecules less than **0·33**.

An alternative to reactions (2), (3), and (4) is reaction (5):



(5)

At high concentrations of retarder, when mutual termination is suppressed, this would lead on the average to 1 initiator fragment and **0·5** retarder molecule combined in each polymer molecule. The amount of combined retarder was a little greater than this in experiments 12 and 15; this may indicate that the radical formed in (1) occasionally reacts with monomer to give a type of copolymerization as shown:



(6)

which could lead to more than **0·5** molecule of retarder on the average in each polymer molecule. This type of behaviour was observered when *p*-benzoquinone was used as a retarder.[4] If the nitro-compound enters the polymer in the way suggested here, it could be removed subsequently by treatment with trifluoroacetic anhydride. Similar considerations can be applied to the mechanisms by which picric acid interferes in radical polymerizations.

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CHEMISTRY DEPARTMENT, BIRMINGHAM UNIVERSITY. [*Received, January 12th*, 1959.]

XUM

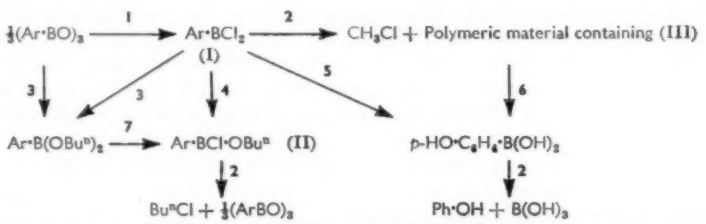
418. *Polycondensations and Certain Other Reactions of Arylboron Chlorides.*

By S. H. Dandegaonker, W. Gerrard, and M. F. Lappert.

Experiments with derivatives of *p*-methoxyphenylboronic acid, phenylboron dichloride, and diphenylboron chloride are described. Two polycondensates have been isolated, which are thermally but not hydrolytically stable. *p*-Hydroxyphenylboronic acid was synthesised from *p*-methoxyphenylboron dichloride.

In the search for thermally and hydrolytically stable semi-inorganic polymers, we have investigated the potentialities of the new compounds *p*-methoxyphenylboron dichloride (I; Ar = *p*-MeO·C_6H_4), *n*-butyl *p*-methoxyphenylchloroboronite (II; Ar = *p*-MeO·C_6H_4), phenylboron dichloride, and diphenylboron chloride.

The experiments in the *p*-methoxyphenylboron series are illustrated by the annexed diagram (Ar = *p*-MeO·C_6H_4); *p*-methoxyphenylboronic anhydride had previously [1] been prepared.



Reagents: 1, BCl_3. 2, Heat. 3, $2Bu^nOH$. 4, Bu^nOH. 5, (*a*) BCl_3, heat; (*b*) H_2O. 6, H_2O (dearylation also occurred giving phenol and boric acid). 7, $ArBCl_2$.

The pyrolysis of *p*-methoxyphenylboron dichloride (I) was expected to produce the polymeric product (III) with elimination of methyl chloride because it has been shown [2] that phenylboron dichloride cleaves ethers, including aralkyl ethers according to: $Ar'OR + PhBCl_2 \longrightarrow Ph{\cdot}BCl{\cdot}OAr' + RCl$. Prolonged heating of *p*-methoxyphenylboron dichloride at 290—300° in fact afforded methyl chloride (100%), a solid, chlorine-containing polymeric material, and hydrogen chloride. The formation of hydrogen chloride can be accounted for by assuming that it arose from a Friedel–Crafts reaction resulting in cross-linking between polymer chains involving attachment of boron atoms from one chain to benzene nuclei of a neighbouring chain. Such a reaction would not be remarkable in view of the high temperature used and because the *p*-methoxyphenylboron dichloride or its polycondensate could act as the electron-deficient catalyst required for a Friedel–Crafts reaction.

$MeO{\cdot}[C_6H_4{\cdot}BCl{-}O]_n{\cdot}C_6H_4{\cdot}BCl_2$ (III) $Ph{-}[BCl{\cdot}C_6H_4{\cdot}]_m{\cdot}BClPh$ (IV)

The polymeric material was readily hydrolysed and the identity of the principal product as *p*-hydroxyphenylboronic acid was established by comparing its characteristics, particularly infrared spectrum, with those of a sample synthesised independently. The presence of boric acid and phenol in the hydrolysis product is accounted for by assuming dearylation during polymerisation; it was also shown that heating *p*-hydroxyphenylboronic acid gave the same products (for similar dearylations see ref. 3).

p-Hydroxyphenylboronic acid, which was unknown at this time, was prepared from

[1] Kuivila and Williams, *J. Amer. Chem. Soc.*, 1954, **76**, 2679; see also König and Scharrnbeck, *J. prakt. Chem.*, 1930, **128**, 157; Bean and Johnson, *J. Amer. Chem. Soc.*, 1932, **54**, 4415.
[2] Dandegaonker, Gerrard, and Lappert, *J.*, 1957, 2893.
[3] Abel, Gerrard, and Lappert, *J.*, 1957, 5051; 1958, 1451.

p-methoxyphenylboron dichloride, as shown in the reaction diagram, and this provides an interesting new use of boron trichloride. The acid has since been obtained by another route.[4]

Pyrolysis of *n*-butyl *p*-methoxyphenylchloroboronite (II) did not result in fission of the methoxy-group, but in slow formation of *p*-methoxyphenylboronic anhydride (see ref. 5 for similar reactions of alkyl phenylchloroboronites).

Diphenylboron chloride was stable at 200—210° (and even at 320°), but in the presence of aluminium chloride benzene equivalent to one group per mol was eliminated. No hydrogen chloride was liberated, as expected from a Friedel–Crafts condensation, and an infusible residue, which may have contained the polymeric material (IV), was obtained.

Phenylboron dichloride, when similarly heated in presence of aluminium chloride was much more stable.

Experimental

Analytical methods have been described previously.[5] Infrared spectral measurements were determined in a Grubb-Parsons S.3A double-beam model with a sodium chloride prism; samples were studied as capillary films or as solid mulls in paraffin oil.

Derivatives of p-*Methoxyphenylboronic Acid.*—*p*-Methoxyphenylboronic acid (26·5 g., 28%) was obtained by a standard procedure from *p*-methoxyphenylmagnesium bromide and tri-*n*-butyl borate (144 g.), and at 110—115° (10 hr.) afforded the anhydride (100%), m. p. 206—207° (Found: B, 8·0. Calc. for $C_7H_7O_2B$: B, 8·0%).

Boron trichloride (15·3 g.) at −39° was added to *p*-methoxyphenylboronic anhydride (17·1 g.) in methylene dichloride–chloroform (1 : 1) (200 c.c) at −80°, and the mixture was stored at −80° for 18 hr. Volatile matter was removed under reduced pressure, and from the residue, p-*methoxyphenylboron dichloride* (68%), m. p. 34—37°, b. p. 85°/0·05 mm. (Found: Cl, 36·8; B, 5·6. $C_7H_7OCl_2B$ requires Cl, 37·5; B, 5·7%), was extracted by 4 : 1 *n*-pentane–methylene dichloride.

By interaction with butan-1-ol (0·90 g.) in methylene dichloride (15 c.c.) at −10°, *p*-methoxyphenylboron dichloride (1·15 g.) afforded *di*-n-*butyl* p-*methoxyphenylboronate* (0·72 g.), b. p. 110—113°/0·3 mm., n_D^{22} 1·4825 (Found: B, 4·0. $C_{15}H_{25}O_3B$ requires B, 4·0%), identical (including infrared spectrum) with the compound obtained (81%), b. p. 105—106°/0·02 mm., n_D^{22} 1·4835 (Found: B, 4·1%), by azeotropic separation of water from a mixture of the anhydride, butan-1-ol, and benzene.

p-Methoxyphenylboron dichloride (9·7 g.) was heated at 225—250° for 50 hr. Methyl chloride (2·1 g., 81%) (Found: Cl, 69·7. Calc. for CH_3Cl: Cl, 70·3%) was condensed at −80°, and hydrogen chloride (1·0 g.) was received in a tube containing pellets of potassium hydroxide. The residue was a glass (5·82 g.) {Found: Cl, 5·8; B, 7·9. Calc. for $[C_6H_4B(Cl)O]_n$: Cl, 25·6; B, 7·8; and for $[C_6H_3B(O)]_m$: B, 10·5%}, which was insoluble in a wide range of organic solvents. The chlorine content of residues obtained in different experiments varied somewhat: *e.g.*, the dichloride (19·33 g.) heated at 290—300° for 70 hr. afforded methyl chloride (5·2 g., 100%), hydrogen chloride (0·64 g.), and a residue (Found: Cl, 14·5; B, 8·8%). In every experiment the Pyrex vessel suffered network fracture beneath the glassy solid, and this was not due to mere thermal treatment of the vessel.

The residues were easily hydrolysed. One residue (4·2 g.) (Found: Cl, 9·3; B, 6·9%) was shaken with water, and the ether-soluble matter, when freed from ether, comprised phenol (0·6 g.) [extracted by *n*-pentane and methylene dichloride (4 : 1)], m. p. 39—40°, b. p. 46—47°/0·1 mm. (trinitro-derivative, m. p. 118—119°) (identified also by its infrared spectrum), and *p*-hydroxyphenylboronic acid (2·45 g.) (Found: B, 7·5. Calc. for $C_6H_7O_3B$: B, 7·8%), m. p. 225—228° unchanged on addition of the specimen obtained as shown below, and having identical infrared spectra. Evaporation of the primary aqueous solution gave boric acid (0·28 g.).

n-*Butyl* p-*methoxyphenylchloroboronite* (1·70 g., 75%), b. p. 83—84°/0·02 mm., n_D^{18} 1·5020 (Found: Cl, 15·8; B, 4·8. $C_{11}H_{16}O_2ClB$ requires Cl, 15·7; B, 4·8%), and hydrogen chloride (0·38 g., 100%) were obtained from *p*-methoxyphenylboron dichloride (1·90 g., 1 mol.) and butan-1-ol (0·76 g., 1 mol.) in methylene dichloride (20 c.c.), which had been mixed at −80°.

[4] Gilman, Santucci, Swayampati, and Ranck, *J. Amer. Chem. Soc.*, 1957, **79**, 3077.
[5] Dandegaonker, Gerrard, and Lappert, *J.*, 1957, 2872.

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The same chloro-ester (1·70 g., 77%), b. p. 85—86°/0·02 mm., n_D^{18} 1·5018, d_4^{20} 1·036 (Found: Cl, 15·5; B, 4·7%), was obtained by mixing the dichloride (0·95 g.) and the dibutyl ester (1·27 g.) at 20°, followed by distillation.

After *n*-butyl *p*-methoxyphenylchloroboronite (2·36 g.) had been heated at 200—220° for 40 hr., part of it (0·80 g., 34%) was recovered (b. p. 84—86°/0·02 mm.) (Found: C., 15·5; B, 4·8%). *p*-Methoxyphenylboronic anhydride (0·90 g.) remained as an involatile residue, and *n*-butyl chloride (0·32 g.) was condensed at −80°. Neither methyl chloride nor hydrogen chloride was detected.

p-*Hydroxyphenylboronic Acid*.—*p*-Methoxyphenylboron dichloride (5·92 g., 1 mol.) and boron trichloride (3·70 g., 1 mol.) were heated at 110—115° for 120 hr. in a sealed tube. After removal of volatile matter at 20°/10 mm., the minimum quantity of water required to dissolve the solid residue was added and the solution was extracted with ether. The ether extract was dried (Na_2SO_4) and freed from solvent at 20°/10 mm. to give *p*-hydroxyphenylboronic acid (4·00 g., 94%), m. p. 210—215° (m. p. 229—232°, after three recrystallisations from methylene dichloride) (Found: C, 51·3; H, 5·38; B, 7·7. Calc. for $C_6H_7O_3B$: C, 52·2; H, 5·10; B, 7·8%). The aqueous portion afforded boric acid (1·99 g., 99%) (Found: B, 17·3. Calc. for H_3O_3B: B, 17·4%) on concentration *in vacuo*. The yields are based on: $MeO{\cdot}C_6H_4{\cdot}BCl_2 + BCl_3 \longrightarrow Cl_2B{\cdot}O{\cdot}C_6H_4{\cdot}BCl_2 + CH_3Cl \xrightarrow{5H_2O} (HO)_3B + HO{\cdot}C_6H_4{\cdot}B(OH)_2$. There was no reaction between the trichloride and *p*-methoxyphenylboron dichloride at 20°.

p-Hydroxyphenylboronic acid (1·73 g.) was heated (80 hr.) with water (0·23 g.) in a sealed tube at 230—240°. The product was shaken with water and 4 : 1 *n*-pentane–ether. Boric acid (0·76 g., 98%) was isolated from the aqueous fraction, and phenol (0·98 g., 91%), b. p. 50—52°/0·2 mm., m. p. 39—40° (trinitro-derivative, m. p. 119°) (identified also by its infrared spectrum), from the organic layer.

Pyrolysis of the Phenylboron Chlorides.—Diphenylboron chloride [6] (5·68 g.) was heated with aluminium chloride (0·20 g.) in a sealed tube at 170—180° for 40 hr. Benzene (1·65 g.), b. p. 80°, n_D^{22} 1·500 (dinitro-derivative, m. p. 89°), was then withdrawn at 60°/11 mm. and condensed at −80°; the residue, except the catalyst, was dissolved in methylene dichloride, and on evaporation of the solvent the solid residue (3·40 g.) [Found: B, 8·7. Calc. for (IV); B, 8·8%] comprised a substance, insoluble in *n*-pentane (0·6 g.) (Found: B, 5·3%), not melting up to 300°, and a sticky gum, soluble in *n*-pentane. When the reaction temperature was 200—210° (80 hr.), benzene (equivalent to removal of one phenyl group) was obtained, and after separation from the catalyst, the final residue contained a substance soluble in water, and another soluble in chloroform; but neither melted up to 300°. When pure diphenylboron chloride was heated at 320° in a sealed tube for 44 hr. subsequent distillation led to 85% recovery of the starting material.

Phenylboron dichloride [6] and aluminium chloride (0·2 g.) were heated at 170—180° (40 hr.) in a sealed tube. The dichloride (4·52 g., 76%), b. p. 58°/11 mm., n_D^{20} 1·5440 (Found: Cl, 43·4; B, 6·7. Calc. for $C_6H_5Cl_2B$: Cl, 44·6; B, 6·9%), was recovered. The residue afforded a gum (extracted with *n*-pentane) and an infusible residue. Hydrogen chloride was not evolved. Similarly half the dichloride was recovered when the temperature was 200—220° and the heating time was 80 hr.

We thank Mr. H. Pyszora for the infrared spectral measurements and the National College of Rubber Technology (Northern Polytechnic) for providing facilities for these.

NORTHERN POLYTECHNIC, HOLLOWAY ROAD,
LONDON, N.7.

[*Received, December 11th*, 1958.]

[6] Abel, Dandegaonker, Gerrard, and Lappert, *J.*, 1956, 4697.

419. *The Kinetics of the Oxidation of Ethane by Nitrous Oxide. Part II.*[1]

By R. KENWRIGHT and A. B. TRENWITH.

A closer examination of the early stages of the reaction between nitrous oxide and ethane within the range 553—588° has enabled the rate constant of the reaction $C_2H_5\cdot + N_2O \longrightarrow C_2H_5{\cdot}O\cdot + N_2$ to be calculated.

Initially hydrogen and ethylene are the major products of the reaction and both are produced at the same rate which, with equal amounts of nitrous oxide and ethane, is about twenty times faster than in the absence of nitrous oxide. The increase may be due to an additional chain-initiating step although " inert " gas effects can also contribute.

The preliminary results of another investigation show that ethylene reacts readily with nitrous oxide at 580°, whereat the separate gases are comparatively stable, the principal non-condensable products being nitrogen, carbon monoxide, and methane.

ON the basis of kinetic measurements the following mechanism has been proposed[1] for the reaction between nitrous oxide and ethane,

$$C_2H_6 \longrightarrow 2CH_3\cdot \quad . \; . \; . \quad (1)$$
$$CH_3\cdot + C_2H_6 \longrightarrow C_2H_5\cdot + CH_4 \quad . \quad (2)$$
$$C_2H_5\cdot \longrightarrow C_2H_4 + H\cdot \quad . \quad (3)$$
$$H\cdot + C_2H_6 \longrightarrow C_2H_5\cdot + H_2 \quad . \quad (4)$$
$$H\cdot + C_2H_5\cdot \longrightarrow C_2H_6 \text{ or } C_2H_4 + H_2 \quad . \; . \quad (5)$$
$$C_2H_5\cdot + N_2O \longrightarrow C_2H_5{\cdot}O\cdot + N_2 \quad . \; . \; . \quad (6)$$
$$C_2H_5{\cdot}O\cdot \longrightarrow CH_3\cdot + CH_2O \quad . \; . \; . \quad (7)$$

From the above it follows that $d[N_2]/d[C_2H_4] = (k_6/k_3)[N_2O]$, so that by comparing the rates of formation of nitrogen and ethylene at various nitrous oxide concentrations it should be possible to derive k_6/k_3. This has been done and in the process further observations have been made on the ethane–nitrous oxide reaction.

EXPERIMENTAL

The materials, apparatus, and procedure were as described before.[1] At first ethylene was determined by absorption in mercuric sulphate–sulphuric acid solution, but early results indicated that the initial rates of formation of hydrogen and ethylene were equal (see Fig. 1), so in subsequent experiments the procedure was simplified, and the non-condensable products only were measured and analysed mass-spectrometrically for hydrogen, carbon monoxide, methane, and nitrogen. The instrument used was a Metropolitan-Vickers, type M.S.2. The electron-accelerating voltage was maintained at 70 ev with a filament current of 100 μA; the ion-accelerating voltage was held constant at 2000 v and automatic magnetic scanning was employed with the recorder unit. An ion-repeller voltage (+12 v) was used in the comparatively stable " plateau " region of the ion-repeller curve; sample volumes were of the order of 0·5 to 1·5 ml. at N.T.P. Cracking patterns and sensitivities of pure components were measured in the usual way and checked at frequent intervals.

The contribution of methane to each spectrum was determined by use of $m/e = 15$ and those of carbon monoxide and nitrogen were estimated by solving two linear simultaneous equations involving $m/e = 28$ and $m/e = 14$. The alternative method for estimating carbon monoxide and nitrogen by using $m/e = 28$ and 29 was tried but proved unreliable.

The actual molar percentage compositions of the mixtures obtained from the pyrolysis of ethane + nitrous oxide varied very little and were of the order: H_2, 60%; N_2, 20%; CH_4, 10%; CO, 10%. Maximum possible errors estimated by analysis of mixtures similar to the above, of known composition, were ±3% of the molar percentage obtained.

RESULTS

Fig. 1 is a typical composition–time graph and represents the products formed from 100 mm. of ethane + 100 mm. of nitrous oxide at 580°. For comparison the hydrogen formed from 100 mm. of ethane alone at the same temperature is also shown.

[1] Part I, Kenwright, Robinson, and Trenwith, *J.*, 1958, 660.

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From the curves the following observations may be made: (*a*) There is a short induction period, not hitherto detected, varying from 16 sec. at 553° to 9 sec. at 588°, and independent of the nitrous oxide concentration; an induction period of the same order of time was observed in the methane–nitrous oxide reaction.[2] It seems likely that these represent the time necessary for chain-carrying radicals to attain steady-state concentrations. Howlett [3] has predicted the existence of induction periods of the same order of magnitude as the above in the pyrolysis of ethane alone. These have not been observed experimentally, probably because below 600° the rate of decomposition of ethane is extremely slow whilst above 600° the induction periods will be too short to be detected. That induction periods have been observed here seems good support of the view that they occur in the decomposition of ethane alone.

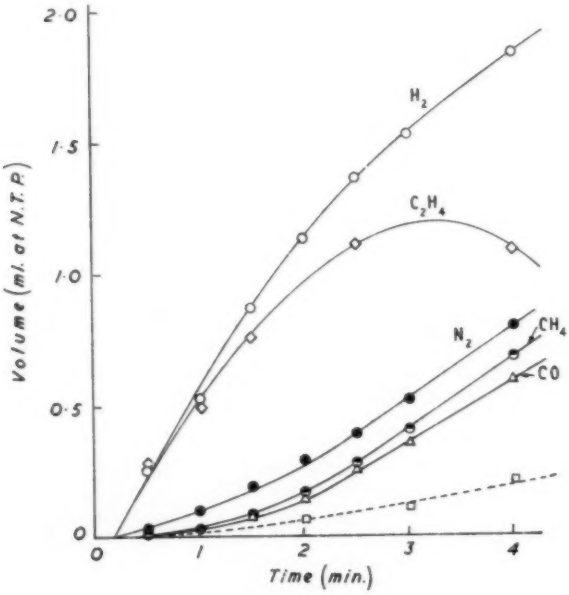

FIG. 1. *Products of pyrolysis of* 100 *mm. of* C_2H_6 + 100 *mm. of* N_2O *at* 580°.

The broken curve represents H_2 from 100 mm. of C_2H_6 alone.

(*b*) The rates of formation of carbon monoxide and methane are initially very low and increase steadily over the first 2½ min. This indicates that (7) is not a fast reaction since both methane and carbon monoxide result from subsequent reactions of the products of (7). The rate of formation of methane slightly exceeds that of carbon monoxide which is to be expected since the latter reacts slowly with nitrous oxide to form nitrogen and carbon dioxide [4] and methane is formed from the methyl radicals produced in both reactions (1) and (7).

(*c*) The initial rates of formation of hydrogen and ethylene are equal. The equality supports the mechanism already advanced since reaction (4) will be rapid and the hydrogen produced by (5) small compared with that formed by (4). The hydrogen formed from the formaldehyde of reaction (7) will be negligible in the early stages of the reaction.

A comparison of the two hydrogen curves, with and without nitrous oxide, shows that an equal volume of the latter increases the initial rate of hydrogen production about twenty-fold.

(*d*) The rate of formation of nitrogen increases with reaction time and this is held to be due to oxidation of primary products by nitrous oxide. Nitrogen is known to be produced by the reaction $CO + N_2O \longrightarrow CO_2 + N_2$, but the shapes of the methane and carbon monoxide curves indicate that only a small fraction of the nitrogen can come from the oxidation of the

[2] Robinson and Smith, *J.*, 1952, **3895**.
[3] Howlett, *Trans. Faraday Soc.*, 1952, **48**, 35.
[4] Bawn, *ibid.*, 1935, **31**, 461.

latter. The other possibility is the ethylene and it is apparent that ethylene decomposes under the experimental conditions but in order to account for the increase in the rate of nitrogen formation with time it is necessary that the rate of formation of nitrogen from ethylene shall be greater than from ethane. From Fig. 2 which shows the reaction products from 100 mm. of ethylene + 100 mm. of nitrous oxide at 580° and, for comparison, the nitrogen from the ethane–nitrous oxide mixture, it may be seen that nitrogen is formed roughly 18 times faster in the ethylene–nitrous oxide system. Comparison of the pressure increase in the reaction vessel with the volumes of non-condensable products produced indicates that the reaction

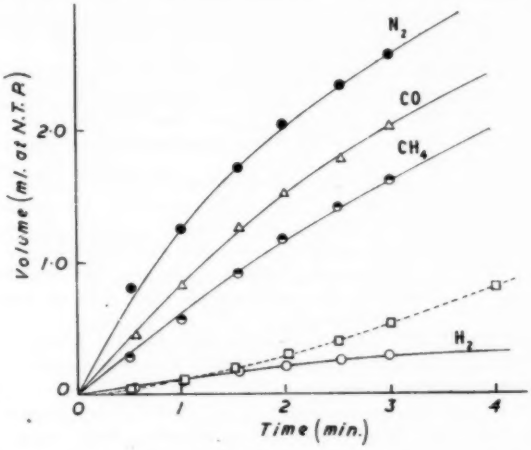

FIG. 2. *Products of pyrolysis of* 100 *mm. of* C_2H_4 + 100 *mm. of* N_2O *at* 580°.

The broken curve represents N_2 from 100 mm. of C_2H_6 + 100 mm. of N_2O.

approximates to $N_2O + C_2H_4 \longrightarrow N_2 + CO + CH_4$ with little, if any, polymerization of the ethylene.

From curves similar to those in Fig. 1 for different initial concentrations of nitrous oxide, values for $d[N_2]/d[C_2H_4]$ were deduced. A plot of these against nitrous oxide concentration was a straight line passing through the origin with a slope corresponding to k_6/k_3. Experiments at 553°, 568·5°, 575°, and 588° provided data for an Arrhenius plot of log k_6/k_3 which was a good straight line: $E_3 - E_6 = 8{\cdot}5$ kcal. mole^{-1} and $A_6/A_3 = 2{\cdot}0$ l. mole^{-1}. Taking E_3 and A_3 as 39·5 kcal. mole^{-1} and 3×10^{14} sec.$^{-1}$ respectively,[5] we have $k_6 = 6 \times 10^{14} \exp(-31{,}000/RT)$ l. mole^{-1} sec.$^{-1}$.

Discussion

The energy of activation of reaction (3) is comparatively high for a radical–molecule reaction but this might be expected as neither methyl radicals nor hydrogen atoms react with nitrous oxide at the experimental temperature.[1]

The most striking observation made during the investigation is the marked increase in the rate of formation of hydrogen when nitrous oxide is present. According to the mechanism suggested $[H\cdot] = k_1k_3k_4/k_5$ so that the rate of formation of hydrogen from (4) should be independent of the nitrous oxide concentration.

One possible explanation of the increase is the occurrence of the additional chain-initiating step $C_2H_6 + N_2O \longrightarrow C_2H_5\cdot + OH\cdot + N_2$. The contribution of this reaction can only be significant, however, if the chains are long, since the formation of hydroxyl radicals must lead to the production of water and none could be detected among the products after prolonged heating of ethane–nitrous oxide mixtures.

A number of " inert " gases increase the rate of decomposition of ethane,[6,7] but with nitrous oxide the magnitude of the increase is such as to rule out the possibility that the

[5] Bywater and Steacie, *J. Chem. Phys.*, 1951, **19**, 326.
[6] Küchler and Thiele, *Z. phys. Chem.*, 1939, *B*, **42**, 359.
[7] Parsons, Danby, and Hinshelwood, *Proc. Roy. Soc.*, 1957, *A*, **240**, 333.

" inert " gas effect is solely responsible, for if this were the case nitrous oxide would transfer energy much more efficiently than ethane itself. The increase in rate of decomposition of ethane may, however, be due partly to the activation of ethane molecules by collision with nitrous oxide.

The authors thank Prof. P. L. Robinson for help and encouragement, Mr. R. E. Dodd for discussions, and Mr. P. Kelly for mass-spectrometric determinations.

KING'S COLLEGE, NEWCASTLE UPON TYNE, 1. [*Received, January 26th*, 1959.]

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420. *The Reactions of Free Benzyl Radicals with* 1 : 2- *and* 3 : 4-*Benzacridine.*

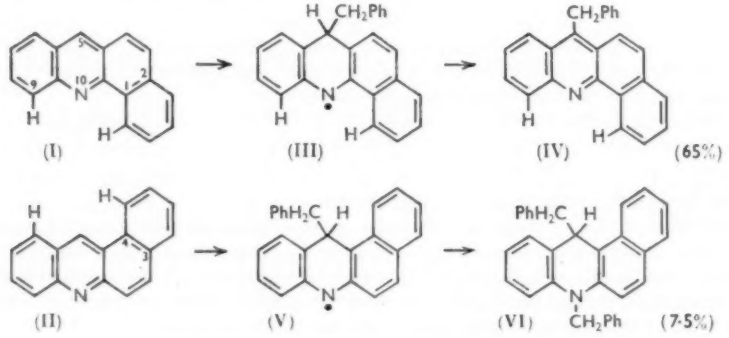
By WILLIAM A. WATERS and D. H. WATSON.

Benzyl radicals have been shown to substitute 1 : 2-benzacridine, in good yield, at the exposed *meso*-position (5) and to a slight extent elsewhere. From the sterically hindered 3 : 4-benzacridine the addition product 5 : 10-dibenzyl-3 : 4-benzacridan was obtained, but only in poor yield. Spatial access of the benzyl radical to the *meso*-position is thus, in both benzacridines, of importance in controlling the courses of reaction.

IN a previous paper [1] we described the reactions of acridine and 5-phenylacridine with benzyl radicals and we now report a similar study with both 1 : 2- and 3 : 4-benzacridine (I and II respectively).

From the reaction of 1 : 2-benzacridine with benzyl radicals a 65% yield of 5-benzyl-1 : 2-benzacridine (IV) was obtained together with a small amount of a dibenzylbenzacridine and 30% of unchanged 1 : 2-benzacridine. From 3 : 4-benzacridine, in contrast, 7·5% of 5 : 10-dibenzyl-3 : 4-benzacridan (VI) was obtained and 75% of unchanged 3 : 4-benzacridine was recovered. In both cases the products found, and possible products which could not be detected in our reaction mixtures, have been synthesised independently by routes that afford conclusive proofs of the structures assigned to them.

Both the reactants yielded considerably more dibenzyl than was obtained in the corresponding reaction with acridine and so must be less reactive radical-acceptors, as would be predicted from approximate calculations of bond localisation energies at the *meso*-carbon centres in the isoconjugate hydrocarbons.[2]



Our previous study with acridine [1] indicated that the initial attack of benzyl radicals on the heterocyclic molecule occurred at the *meso*-carbon atom rather than at the nitrogen

[1] Waters and Watson, *J.*, 1957, 253.
[2] Dewar, *J. Amer. Chem. Soc.*, 1952, **74**, 3357.

atom, and our present results support this conclusion but are of added interest in that they illustrate the significance of steric hindrance to homolytic substitution. In 1 : 2-benzacridine (I) the *meso*-carbon (5) is sterically unhindered, whilst the nitrogen atom is hindered. Consequently radical (III) may easily be formed and its homolytic dehydrogenation (by a second benzyl radical) to (IV) would occur more easily than the addition of a second benzyl radical to the nitrogen. 3 : 4-Benzacridine (II) is of a converse structural type; radical addition to give (V) is difficult, but thereafter the second radical can easily add to yield a benzacridan derivative (VI), though in very low overall yield. Alternatively, compound (VI) might be produced by initial addition of a benzyl radical to the unhindered nitrogen atom of 3 : 4-benzacridine. Evidence that such addition is possible is presented by us in the following paper.

At the inception of this work it was hoped that some evidence of radical attack at the " K " (phenanthrenoid) positions might be discovered, corresponding to the substitution of 5-phenylacridine in the 1-position. The dibenzylacridine isolated from 1 : 2-benzacridine (I) is perhaps formed by a reaction of this type.

Experimental

1 : 2-Benzacridine was prepared from 5-chloro-1 : 2-benzacridine,[3] m. p. 144—145°. This was reduced to 1 : 2-*benzacridan* [Found: C, 88·4; H, 5·7; N, 6·1. $C_{17}H_{13}N$ requires C, 88·2; H, 5·7; N, 6·2%), $\lambda_{max.}$ 2580, 2840, 3500 Å (log ε 4·29, 4·06, 3·97) in ethanol], (yellow plates from aqueous ethanol; m. p. 140°) with hydrogen and Raney nickel in alkaline ethanol.[4] The 1 : 2-benzacridan was then oxidised in boiling water with potassium dichromate and sulphuric acid by the method described by Albert and Willis [5] for the oxidation of 3 : 4-benzacridan. 1 : 2-Benzacridine was thus obtained in 75% yield as lemon-yellow needles (from *cyclo*hexane), m. p. 107—108° (lit.,[6] 108°), $\lambda_{max.}$ in ethanol 2675, 2740, 2850, 3315, 3380, 3415, 3645, 3840 Å (log ε 4·75, 4·90, 4·69, 3·78, 3·78, 3·84, 3·93, 3·96). It was easily reduced to 1 : 2-benzacridan (yield 75%) by treatment with lithium aluminium hydride in boiling tetrahydrofuran (2% solution).

Preparations of 3 : 4-benzacridine by the reactions of Ullmann and Fetvadjian [7] and of Buu-Hoï [8] gave variable and uncertain yields. A much more certain route was that of ring closure of *N*-2′-naphthylanthranilic acid [9] to 5-chloro-3 : 4-benzacridine,[3] reduction of this to 3 : 4-benzacridan, m. p. 166—168°, $\lambda_{max.}$ in ethanol, 2680, 2780, 3160, 3675 Å (log ε 4·34, 4·40, 4·09, 3·57), with hydrogen and Raney nickel, as described by Badger, Seidler, and Thomson,[4] and oxidation of the latter in boiling water with potassium dichromate and sulphuric acid as described by Albert and Willis.[5] The 3 : 4-benzacridine crystallised from *cyclo*hexane in white needles, m. p. 131° (lit., 131°), $\lambda_{max.}$ in ethanol 2765, 2850, 3365, 3465, 3635, 3835 Å (log ε 4·76, 4·73, 3·77, 3·88, 4·00, 4·03).

Reaction of 1 : 2-*Benzacridine with Benzyl Radicals.*—1 : 2-Benzacridine (4·5 g.) in dry toluene (400 ml.) was refluxed under nitrogen with *tert.*-butyl peroxide (8·2 g.) for 76 hr. After evaporation of the solvent the residual gum (9 g.), in light petroleum (200 ml.), was chromatographed on alumina (600 g.) with light petroleum–benzene. It gave (*a*) dibenzyl(1·6 g.), (*b*) 1 : 2-benzacridine (1·4 g., 31%), yellow needles (from *cyclo*hexane), m. p. and mixed m. p. 107°, (*c*) 5-benzyl-1 : 2-benzacridine (4·0 g., 64%) which crystallised from *cyclo*hexane in pale yellow needles, m. p. and mixed m. p. (see below) 144° (Found: C, 89·8; H, 5·2; N, 4·6. Calc. for $C_{24}H_{17}N$: C, 90·2; H, 5·4; N, 4·4%), $\lambda_{max.}$ in ethanol 2680, 2780, 2885, 3350, 3490, 3670, 3865 Å (log ε 4·79, 4·97, 4·94, 3·89, 3·99, 4·05, 4·03), and (*d*) a gum (0·75 g.) which after extraction with 2N-sulphuric acid, basification, and further chromatography gave a *dibenzyl*-1 : 2-*benzacridine* (80 mg., 1%) which crystallised from *cyclo*hexane in pale yellow needles, m. p. 177·5—179° (corr.) (Found: C, 90·8; H, 5·7; N, 3·7. $C_{31}H_{23}N$ requires C, 90·9; H, 5·7; N, 3·4%). The infrared absorption of the

[3] Bachmann and Picha, *J. Amer. Chem. Soc.*, 1946, **68**, 1599.
[4] Cf. Badger, Seidler, and Thomson, *J.*, 1951, 3207.
[5] Albert and Willis, *J. Soc. Chem. Ind.*, 1946, **65**, 26.
[6] Ullmann and La Torre, *Ber.*, 1904, **37**, 2922.
[7] Ullmann and Fetvadjian, *Ber.*, 1903, **36**, 1029.
[8] Buu-Hoï, *J.*, 1949, 670.
[9] Ullmann, *Annalen*, 1907, **355**, 350. (This is best prepared by a Chapman reaction; cf. ref. 1.)

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last compound at 698, 709, and 753 cm.$^{-1}$ indicates the presence of phenyl and its absorption in chloroform [$\lambda_{max.}$ 2740, 2840, 2950, 3380, 3435, 3540, 3715, 3920 Å (log ε 4·54, 4·72, 4·75, 3·76, 3·76, 3·80, 3·87, 3·76)] indicates that it is a substituted 1 : 2-benzacridine. A trace of a colourless benzyl-1 : 2-benzacridine (structure inferred from light absorption), m. p. 194—197°, was also obtained.

Reaction of 3 : 4-*Benzacridine with Benzyl Radicals.*—3 : 4-Benzacridine (6 g.), toluene (300 ml.), and *tert.*-butyl peroxide (6·7 g.) were refluxed under nitrogen for 9 days. Investigation of the product, as described above, established the presence of dibenzyl (5 g.), 3 : 4-benzacridine (4·2 g., 70%), and 5 : 10-*dibenzyl*-3 : 4-*benzacridan* (0·81 g., 7·5%). The last crystallised from methanol–methyl acetate in white needles, m. p. and mixed m. p. 157—159° (Found: C, 90·3; H, 6·0; N, 3·2. $C_{31}H_{25}N$ requires C, 90·5; H, 6·1; N, 3·4%), $\lambda_{max.}$ 2765, 3165, 3600 Å (log ε 4·56, 4·18, 3·64), inflexions at 2675, 3060 Å (log ε 4·47, 4·11) (*i.e.*, absorption of acridan type).

Preparations of Reference Compounds.—5-Benzyl-1 : 2-benzacridine, prepared by fusion of *N*-phenyl-1-naphthylamine and phenylacetic acid with zinc chloride,[8] had m. p. 143—144° [picrate, m. p. 225—256° (decomp.)]. 5-*Benzyl*-1 : 2-*benzacridan*, obtained by reduction of this compound with lithium aluminium hydride in tetrahydrofuran, crystallised from light petroleum in needles, m. p. 125° (Found: C, 89·7; H, 6·0; N, 4·7. $C_{24}H_{19}N$ requires C, 89·7; H, 6·0; N, 4·4%), $\lambda_{max.}$ in ethanol 2600, 3465 Å (log ε 4·32, 3·98).

5-Benzyl-1 : 2-benzacridan (0·18 g.) was added with stirring to a solution of potassamide (from 0·13 g. of potassium and a trace of ferric nitrate) in liquid ammonia (130 ml.). After 30 min. the dark colour of the solution was discharged by dropwise addition of benzyl chloride and, after evaporation of the ammonia, the excess of benzyl chloride was removed in steam. The residue was taken up in light petroleum–benzene (1 : 1) and filtered through alumina. After recrystallisation from methanol–methyl acetate the 5 : 10-*dibenzyl*-1 : 2-*benzacridine* (0·12 g.) formed needles, m. p. 123—124° (Found: C, 90·8; H, 6·1; N, 3·4. $C_{31}H_{25}N$ requires C, 90·5; H, 6·1; N, 3·4%), $\lambda_{max.}$ in ethanol 2545, 3375 Å (log ε 4·31, 3·89).

5-Benzyl-3 : 4-benzacridine,[8] prepared by fusion at 215—240° of *N*-phenyl-2-naphthylamine,[10] phenylacetic acid, and zinc chloride, had m. p. 143° (from light petroleum) (Found: C, 90·2; H, 5·2; N, 4·2. Calc. for $C_{24}H_{17}N$: C, 90·2; H, 5·4; N, 4·4%), $\lambda_{max.}$ in ethanol 2480, 2780, 2850, 3510, 3685, 3880 Å (log ε 4·41, 4·83, 4·81, 3·93, 4·01, 3·97).

5-Benzyl-3 : 4-benzacridine (2·15 g.) in boiling toluene (100 ml.) was treated with sodium (10·5 g.), and pentanol (100 ml.) was gradually added. When the sodium had dissolved the solution was cooled, washed with water, and evaporated. Crystallisation of the residue from methanol gave 5-*benzyl*-1′ : 2′ : 3′ : 4′-*tetrahydro*-3 : 4-*benzacridan*, m. p. 156—157° (1 g.) (Found: C, 88·6; H, 7·2; N, 4·3. $C_{24}H_{23}N$ requires C, 88·6; H, 7·1; N, 4·3%). Its light absorption in ethanol, $\lambda_{max.}$ 2830 Å (log ε 4·15), indicates that it contains an acridan and not a benzacridan system. The same compound was obtained (yield 95%; m. p. 156—157°) by reducing 5-benzyl-3 : 4-benzacridine with excess of sodium in liquid ammonia. Oxidation of this substance (50 mg.) in aqueous alcohol with ferric chloride at 100° gave yellow needles, m. p. 117—119°, $\lambda_{max.}$ in ethanol 2565, 3575 Å (log ε 5·34, 4·15) (indicative of 5-benzyl-1′ : 2′ : 3′ : 4′-tetrahydro-3 : 4-benzacridine).

5-*Benzyl*-3 : 4-*benzacridan* was obtained by reducing 5-benzyl-3 : 4-benzacridine (1·0 g.) with lithium aluminium hydride (0·4 g.) in refluxing tetrahydrofuran (30 ml.) for 14 hr. and then decomposing the excess of reducing agent with ethyl acetate. It crystallised from methanol–methyl acetate in needles, m. p. 138—140° (0·75 g.) (Found: C, 89·7; H, 5·9; N, 4·1. $C_{24}H_{19}N$ requires C, 89·7; H, 6·0; N, 4·4%), $\lambda_{max.}$ in ethanol 2735, 3080, 3635, 3815 Å (log ε 4·56, 4·06, 3·63, 3·53). Benzylation of this in liquid ammonia, with potassamide and benzyl chloride as described above, gave 5 : 10-dibenzyl-3 : 4-benzacridan, wich crystallised from methanol in needles, m. p. 161—163° (Found: C, 90·4; H, 5·9; N, 3·8. Calc. for $C_{31}H_{25}N$: C, 90·5; H, 6·1; N, 3·4%), $\lambda_{max.}$ in ethanol 2680, 2770, 3065, 3160, 3600 Å (log ε 4·47, 4·56, 4·11, 4·18, 3·64).

One of us (D. H. W.) thanks the Department of Scientific and Industrial Research for a research studentship (this and the following paper).

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, January 6th,* 1959.]

[10] Knoevenagel, *J. prakt. Chem.*, 1914, **89**, 17.

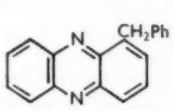
421. *The Reaction of Phenazine with Free Benzyl Radicals.*

By WILLIAM A. WATERS and D. H. WATSON.

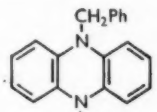
Benzyl radicals react easily with phenazine, giving 1-benzylphenazine and 5 : 10-dibenzyl-5 : 10-dihydrophenazine in the approximate ratio 3 : 1. *C*-Substituted di- and possibly tetra-benzylphenazines are also formed.

WORK in this laboratory has shown that benzyl radicals add to the *meso*-positions of anthracene [1] and acridine; [2] in the latter case the initial attack occurred at the carbon and not at the nitrogen centre, an inference corroborated by investigation of the 1 : 2- and 3 : 4-benzacridine.[3] It was therefore of interest to investigate the benzylation of phenazine in which nitrogen occupies both *meso*-positions.

Phenazine proved very reactive since only about 1% of dibenzyl was formed by combination of benzyl radicals. The reaction yielded 1-benzylphenazine (I) and 5 : 10-dibenzyl-5 : 10-dihydrophenazine (II) in the approximate molar ratio of 3 : 1 and smaller amount of more highly *C*-substituted phenazines, but no trace of 2-benzylphenazine



(I)



(II)

was discovered. For reference, authentic 1- and 2-benzylphenazine were synthesised by oxidising 1- and 2-methylphenazine [4,5] to the corresponding aldehydes, condensing these with phenylmagnesium bromide, oxidising the resulting alcohols to the benzoylphenazines, and reducing the latter by the Huang-Minlon method. 5 : 10-Dibenzyl-5 : 10-dihydrophenazine was prepared by benzylating the sodium adduct of phenazine.[6]

The theoretical implications of this study are two-fold. First, it gives clear evidence of some direct attack of hydrocarbon radicals on the nitrogen atoms of heterocyclic aromatic ring-systems, a feature of homolytic substitution that has not been established with pyridine or quinoline and was thought not to occur with acridine,[2] though the possibility of attack by benzoylperoxy-radicals on the nitrogen of pyridine and quinoline has recently been considered.[7] Secondly, it shows that phenazine is much more reactive in the side rings than anthracene or acridine, combined with which is its marked tendency to form *C*-substitution rather than addition products and thus preserve the aromatic character of the whole molecule. Substitution in α- rather than in β-positions naturally accords with qualitative theoretical expectations.

EXPERIMENTAL

M. p.s are corrected.

Phenazine was prepared from 2-nitrodiphenylamine in 60% yield by Waterman and Vivian's method.[8]

Reactions with Benzyl Radicals.—(i) Phenazine (5 g.) and *tert.*-butyl peroxide (8·2 g., 2 mol.) were refluxed under nitrogen in dry toluene (400 ml.) for 7 days. After removal of solvent the residual black gum (9·4 g.) was taken up in light petroleum–benzene (9 : 1) and chromatographed

[1] Beckwith and Waters, *J.*, 1957, 1001.
[2] Waters and Watson, *J.*, 1957, 253.
[3] Waters and Watson, preceding paper.
[4] McCombie, Scarborough, and Waters, *J.*, 1928, 353.
[5] Vivian, Hartwell, and Waterman, *J. Org. Chem.*, 1954, **19**, 1641.
[6] Mikhailov and Blokhina, *Izvest. Acad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1950, 304; *Chem. Abs.*, 1950, **44**, 9452.
[7] Pausacker, *Austral. J. Chem.*, 1958, **11**, 200.
[8] Waterman and Vivian, *J. Org. Chem.*, 1949, **14**, 289.

through alumina (300 g.). It yielded green-grey needles (260 mg.) which after sublimation at 200°/0·5 mm. and crystallisation from light petroleum gave yellow needles of 5 : 10-*dibenzyl*-5 : 10-*dihydrophenazine*, m. p. and mixed m. p. (see below) 213—214·5° (Found: C, 86·6; H, 6·3; N, 7·5. $C_{26}H_{22}N_2$ requires C, 86·2; H, 6·1; N, 7·7%). Further elution with benzene gave mixtures of phenazine and benzylphenazines. From further similar experiments, this mixture was separated by steam-distillation into a trace of dibenzyl (<2%), volatile phenazine, m. p. and mixed m. p. 173—174°, and involatile 1-*benzylphenazine*, yellow needles (from light petroleum), m. p. and mixed m. p. (see below) 120—121° (Found: C, 84·0; H, 5·1; N, 10·4. $C_{19}H_{14}N_2$ requires C, 84·4; H, 5·2; N, 10·4%), which was oxidised by chromium trioxide in acetic acid to 1-*benzoylphenazine*, yellow needles (from methanol), m. p. and mixed m. p. 196—197° (Found: C, 80·1; H, 4·3; N, 10·2. $C_{19}H_{12}ON_2$ requires C, 80·2; H, 4·3; N, 9·9%). There were also isolated from the involatile material a *dibenzylphenazine* (2·5%) crystallising in yellow needles, m. p. 171—173° (Found: C, 86·7; H, 5·7; N, 7·5. $C_{26}H_{20}N_2$ requires C, 86·7; H, 5·6; N, 7·8%), and a smaller amount of a *tetrabenzylphenazine*, as yellow needles, m. p. 198—200° (Found: C, 88·8 ± 0·4; H, 6·0 ± 0·7; N, 4·7 ± 0·5 in 5 analyses. $C_{40}H_{32}N_2$ requires C, 88·8; H, 6·0; N, 5·2%).

(ii) Phenazine (10 g.) and *tert.*-butyl peroxide (8 g., 0·9 mol.) were refluxed under a stream of pure nitrogen in dry toluene (500 ml.) for 76 hr. Steam-distillation of the resulting material separated 5·8 g. (58%) of phenazine and by chromatography there were obtained 1 g. (5%) of 5 : 10-dibenzyl-5 : 10-dihydrophenazine, 2·5 g. (16·5%) of 1-benzylphenazine, and traces of yellow polybenzylphenazines with m. p.s in the range 205—220°. None of the infrared spectra of these fractions had a band at 814 $cm.^{-1}$ indicative of 2-benzylphenazine.

The dibenzylphenazine of m. p. 171—173° is not 1 : 4-dibenzylphenazine, which is known;[9] it may well be 1 : 5-dibenzylphenazine.

Preparation of Reference Compounds.—1-Methylphenazine, m. p. 107—108° (lit., 108°), was obtained in 37% yield by heating 2-methyl-2′-nitrodiphenylamine[4] with 10 times its weight of degreased iron filings (cf. ref. 8) and then oxidised with freshly sublimed selenium dioxide to 1-formylphenazine, m. p. 176—177° (lit.,[10,11] 175°), by Rozum's method.[10] To this aldehyde (2 g.) in tetrahydrofuran (200 ml.) was added, under nitrogen, a filtered solution of phenylmagnesium bromide (from 6 g. of bromobenzene) in ether. After completion of the reaction the product, 1-α-*hydroxybenzylphenazine* (1·4 g.), was purified chromatographically and crystallised from methanol in fine yellow needles, m. p. 126—127° (Found: C, 79·8; H, 4·8; N, 9·9. $C_{19}H_{14}ON_2$ requires C, 79·7; H, 4·9; N, 9·8%). This alcohol (0·3 g.) was oxidised at 100° with chromium trioxide (0·1 g.) in acetic acid (4 ml.) to 1-benzoylphenazine (0·18 g.) which crystallised from methanol in stout yellow needles, m. p. 196—197° (Found: C, 80·4; H, 4·6; N, 9·6%). This material (0·18 g.) was reduced with 100% hydrazine hydrate (2 ml.) and potassium hydroxide (1·5 g.) in diethylene glycol (10 ml.) and gave 1-benzylphenazine (0·15 g.) as yellow needles [from light petroleum (b. p. 40—60°)], m. p. 121—122° (Found: C, 84·7; H, 5·1; N, 10·1%).

Phenazine	$\lambda_{max.}$ (Å)	log ε	$\lambda_{max.}$ (Å)	log ε
1-Methyl ...	2515	5·2	3630	4·2
2-Methyl ...	2515	5·2	3645	4·2
1-Benzyl ...	2520	5·1	3635	4·2
1-Benzoyl	2490	5·0	3645	4·2
2-Benzyl ...	2565	5·0	3650	4·2

Phenazine	$\lambda_{max.}$ (Å)	log ε	$\lambda_{max.}$ (Å)	log ε
Dibenzyl (m. p. 171—173°)	2565	5·0	3650	4·2
Tetrabenzylphenazine (m. p. 199—200°)	2670	—	3730	—
5 : 10-Dibenzyl-5 : 10-dihydro	2500	4·9	2530*	4·8
	3530	4·0	3590*	4·0

* In chloroform.

From 2-methylphenazine, m. p. 117—118° (lit.,[4] 117°), prepared similarly from 4-methyl-2′-nitrodiphenylamine, was obtained 2-formylphenazine, m. p. 187° (corr.) (lit.,[10] 185°), and thence 2-α-*hydroxybenzylphenazine* which crystallised from methanol in yellow plates, m. p. 174—174·5° (Found: C, 79·8; H, 5·0; N, 9·6%). Oxidation of this, as described above, gave 2-*benzoylphenazine*, yellow needles (from methanol), m. p. 130—131° (Found: C, 70·8; H, 4·2; N, 9·6%), from which by Huang-Minlon reduction was obtained 2-*benzylphenazine*, yellow needles (from light petroleum), m. p. 106—107·5° (Found: C, 84·7; H, 5·3; N, 10·1%).

[9] McIlwain, *J.*, 1937, 1701.
[10] Rozum, *Zhur. obshchei Khim.*, 1955, **25**, 611.
[11] Birkofer and Birkofer, *Chem. Ber.*, 1952, **85**, 286.

5 : 10-Dibenzyl-5 : 10-dihydrophenazine was prepared by adding sodium chips (1·8 g.) to a stirred suspension of phenazine (1·75 g.) in liquid ammonia (300 ml.); after 45 min. the deep blue colour was discharged by addition of benzyl chloride, ammonia was allowed to evaporate from the resulting yellow solution, and the remainder after treatment with water was steam-distilled. From the residue (2·3 g.) the dibenzyldihydrophenazine crystallised on addition of benzene and had m. p. and mixed m. p. 213—214·5° with material obtained from the reaction described above. The same substance was obtained in 44% yield by shaking phenazine (1·1 g.), sodium (0·4 g.), and glass chips in 1 : 2-dimethoxyethane (20 ml.) under nitrogen for 36 hr.[6] and then decomposing the sodium adduct with benzyl chloride; this had m. p. 213—214·5° (Found: C, 86·3; H, 6·2; N, 7·7%).

Ultraviolet Spectra of Phenazine Derivatives in Ethanol.—These are reported in the Table.

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422. *Experiments towards the Synthesis of Corrins. Part I. The Preparation and Reactions of Some Δ^1-Pyrrolines. A Novel Proline Synthesis.*

By R. BONNETT, V. M. CLARK, A. GIDDEY, and SIR ALEXANDER TODD.

Several Δ^1-pyrrolines have been prepared by cyclisation of γ-amino-carbonyl compounds and by dehydrogenation of pyrrolidines with mercuric acetate. Their reactions with various nucleophiles have been studied. Addition of hydrogen cyanide to Δ^1-pyrrolines unsubstituted in the 2-position gives 2-cyanopyrrolidines which can be hydrolysed to the corresponding proline derivatives.

THE molecule of vitamin B_{12} contains a planar quadridentate ligand bearing a resemblance to the porphyrins, though at a lower level of oxidation.[1] For the basic ring system (I) of this ligand the name "corrin" has been proposed.[2] This ring system has as yet been found only in the B_{12} group of vitamins and in an endeavour to further our understanding of the vitamin and its mode of action experiments towards the synthesis of corrin derivatives have been initiated and will be reported in this and subsequent papers.

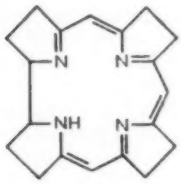
The unit ring system of the corrin nucleus is related to the Δ^1-pyrrolines, about which little is known. This lack of knowledge is doubtless due in part to the difficulty encountered by earlier workers in determining the true position of the double bond in their products. The reduction of pyrroles with zinc in acid solution[3] appears to yield Δ^3-pyrrolines as major products, together with some of the Δ^1-form, though catalytic isomerisation using Raney nickel[4] converts Δ^3- into the Δ^1-isomers. A more widely applicable preparative method has been that based upon the cyclisation of γ-amino-carbonyl compounds.[5] Using this route we have prepared a series of Δ^1-pyrrolines (III, a, b, c). In each case, before reduction of the nitro-group, the carbonyl group was protected as the 1 : 3-dioxolan derivative in order to avoid formation of the corresponding pyrrolidine and Δ^1-pyrroline 1-oxide.[6] The Δ^1-pyrrolines so obtained are colourless volatile liquids having a penetrating and unpleasant odour. They can be readily characterised as their picrates. The infrared spectra of the liquid bases show a strong absorption band, attributable to the C=N stretching mode, appearing near 1650 or 1620 cm.$^{-1}$ depending on whether or not the =C– atom bears an alkyl substituent. Protonation of the azomethine group gives rise to a

[1] Bonnett, Cannon, Clark, Johnson, Parker, Lester Smith, and Todd, *J.*, 1957, 1158, and references therein cited.
[2] I.U.P.A.C. "Nomenclature of Organic Chemistry, 1957," Butterworths, 1958, p. 85.
[3] Ciamician and Dennstedt, *Ber.*, 1882, **15**, 1831.
[4] Evans, *J. Amer. Chem. Soc.*, 1951, **73**, 5230.
[5] Kohler and Drake, *ibid.*, 1923, **45**, 2144; Cloke, *ibid.*, 1929, **51**, 1174; Rupe and Gisiger, *Helv. Chim. Acta*, 1925, **8**, 338.
[6] Cf. Knott, *J.*, 1948, 186; Kloetzel and Pinkus, *J. Amer. Chem. Soc.*, 1958, **80**, 2332.

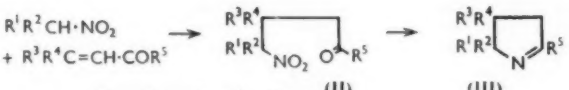
XUM

hypsochromic shift of approximately 35 cm.$^{-1}$, the band being readily observable with hydrochlorides though not always with picrates where absorption due to the anion tends to be superimposed upon it. In conformity with the Δ^1-formulation the infrared spectra of the free bases show no absorption of an N–H stretching mode and electrometric titration in aqueous solution gives pK_a values of 6·7—7·7, as would be expected of Schiff bases.[7]

In the absence of specific evidence to the contrary, it might be assumed that those pyrrolines formed by the cyclisation of γ-amino-ketones would have been formulated in the existing literature as the Δ^1-isomers. However, both Hielscher [8] and Gabriel [9] assigned



(I)



	R^1	R^2	R^3	R^4	R^5
(a)	Me	Me	H	H	H
(b)	Me	Me	Me	H	H
(c)	H	H	Me	Me	Me

(II) (III)

the Δ^2-structure to such products and Sonn,[10] although expressing the possibility of tautomerism between Δ^1- and Δ^2-forms, formulated the stable product as the Δ^2-isomer. As a result the very existence of Δ^1-pyrrolines was denied in some texts [11] and it is only recently that compelling spectral evidence for the Δ^1-formulation of these reduction products has been presented.[4,12]

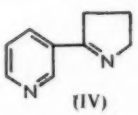
In addition to the above reductive methods it has now proved possible to obtain Δ^1-pyrrolines by dehydrogenation of the corresponding pyrrolidines. The dehydrogenation of tertiary amines has been extensively investigated by using a variety of reagents; [13-18] secondary amines have, however, received much less attention. *N*-Methylbenzylamine has been dehydrogenated with manganese dioxide in chloroform,[19] and evidence for the formation of an azomethine group obtained though the Schiff base was not isolated; the same reagent has been shown to convert *N*-methylaniline into formanilide.[18] Piperidine, on attempted conversion into Δ^1-piperideine, yielded a series of trimers [20] and analogous behaviour in the case of pyrrolidine has been reported.[21]

In the present work we have found that a number of cyclic secondary amines can be dehydrogenated by mercuric acetate in dilute aqueous acetic acid. This reagent, under somewhat milder conditions, has been used by Leonard and his co-workers [14] for the dehydrogenation of cyclic tertiary amines, their conditions being such that secondary amines were unaffected.[22] In our experiments the reaction was conveniently followed by

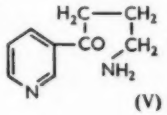
[7] Starr, Bulbrook, and Hixon, *J. Amar. Chem. Soc.*, 1932, **54**, 3971.
[8] Hielscher, *Ber.*, 1898, **31**, 277.
[9] Gabriel and Colman, *Ber.*, 1908, **41**, 513; Gabriel, *ibid.*, 1909, **42**, 1238.
[10] Sonn, *Ber.*, 1935, **68**, 148; 1939, **72**, 2150.
[11] Sidgwick, Taylor, and Baker, "The Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 1937, p. 491; Corwin in "Heterocyclic Compounds," ed. Elderfield, Wiley, New York, 1950, Vol. I, p. 339.
[12] Eddy and Eisner, *Analyt. Chem.*, 1954, **26**, 1428; Witkop, *J. Amer. Chem. Soc.*, 1954, **76**, 5597.
[13] Julian and Printy, *ibid.*, 1949, **71**, 3206; Buckley, Dunstan, and Henbest, *J.*, 1957, 4880.
[14] Leonard and Hauck, *J. Amer. Chem. Soc.*, 1957, **79**, 5279, and references therein.
[15] Buckley, Dunstan, and Henbest, *J.*, 1957, 4901.
[16] Dunstan and Henbest, *ibid.*, 4905.
[17] Godtfredsen and Vangedal, *Acta Chem. Scand.*, 1956, **10**, 1414.
[18] Henbest and Thomas, *J.*, 1957, 3032.
[19] Highet and Wildman, *J. Amer. Chem. Soc.*, 1955, **77**, 4399.
[20] Lehmann and Schwaderer, *Ber.*, 1889, **22**, 1318, 1328; Schöpf, Komak, Braun, and Jacobi, *Annalen*, 1948, **559**, 1, and later papers.
[21] Schöpf, F.I.A.T. Review, "Preparative Organic Chemistry," 1948, Part 2, p. 117.
[22] Leonard and Morrow, *J. Amer. Chem. Soc.*, 1958, **80**, 371.

observing the precipitation of mercurous acetate, and the products were examined by gas-chromatography which separated the 2-alkylpyrrolidines clearly from the corresponding Δ^1-pyrrolines: the latter were readily isolated as picrates. In this fashion, 2-methylpyrrolidine, 2 : 5-dimethylpyrrolidine, and 2 : 4 : 4-trimethylpyrrolidine were dehydrogenated, the crude product in each case containing the original base and the corresponding Δ^1-pyrroline in approximate ratio 3 : 2. The nature of the unsaturated products was confirmed by their electrometric titration curves and infrared spectra, and by the mixed melting points of their picrates. In the case of pyrrolidine itself, mercurous acetate was precipitated during the reaction but no new volatile base could be isolated: presumably the product polymerised.[23] 2 : 2-Dimethylpyrrolidine and 2 : 2 : 3-trimethylpyrrolidine were not dehydrogenated under these conditions, whilst 2-methylpiperidine gave a low yield of 2-methylpiperideine. In the pyrrolidine series, not only is a planar *transoid* arrangement unfavourable, but initial mercuration is subject to considerable steric hindrance when an α-position is completely substituted.

The Δ^1-pyrrolines, on the basis of their analyses, infrared spectra, and low basicity, exist in the cyclic form rather than as acyclic γ-amino-carbonyl compounds, although with acylating agents derivatives of the acyclic form are obtained.[9] The tobacco-smoke constituent, myosmine [24] (IV), readily yields carbonyl derivatives [25] although the existence of the amino-ketone poikiline [26] (V) as such is open to question.

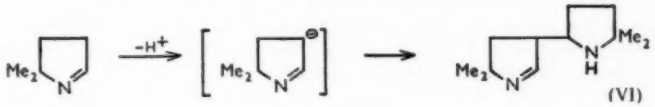


(IV)



(V)

Δ^1-Pyrrolines are slowly reduced by tin and hydrochloric acid and, more rapidly, by lithium aluminium hydride to yield, in each case, the pyrrolidine. The azomethine link is much less susceptible to nucleophilic addition than the carbonyl group, though under acid conditions reactivity is enhanced. Under basic conditions, nitromethane and nitroethane did not react with any of the Δ^1-pyrrolines investigated, nor did addition of the Grignard reagent occur. Previous workers have used the Grignard reagent in attempted Zerewitinow determinations on 2-substituted Δ^1-pyrrolines: the formation of a 1 : 1 complex has been reported [27] and in some instances the pyrroline has been recovered.[27,28]



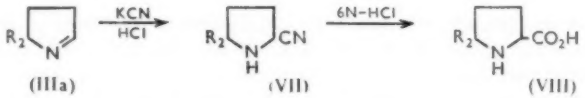
(VI)

In the present work, attempted addition of ethylmagnesium bromide to 2 : 4 : 4-trimethyl-Δ^1-pyrroline led to a trace of high-boiling material and 40% recovery of the base. 5 : 5-Dimethyl-Δ^1-pyrroline behaved differently, and there is evidence that the high-boiling product contained the dimeric compound (VI) formed, probably, as a result of initial abstraction of a proton followed by addition to a second pyrroline molecule.[29]

The addition of cyanide ion to a protonated or quaternised azomethine is well

[23] Fuhlhage and VanderWerf, *J. Amer. Chem. Soc.*, 6249.
[24] Späth, Wenusch, and Zajic, *Ber.*, 1936, **69**, 393; Stein and Burger, *J. Amer. Chem. Soc.*, 1957, **79**, 154.
[25] Haines, Eisner, and Woodward, *ibid.*, 1945, **67**, 1258.
[26] Wenusch and Schöller, quoted by Marion, "The Alkaloids," ed. Manske and Holmes, Academic Press, New York, 1950, Vol. I, p. 256.
[27] Maginnity and Cloke, *J. Amer. Chem. Soc.*, 1951, **73**, 49; Maginnity and Gair, *ibid.*, 1952, **74**, 4958.
[28] Kloetzel, Pinkus, and Washburn, *ibid.*, 1957, **79**, 4222.
[29] Cf. Short and Watt, *J.*, 1930, 2293; Plancher and Ravenna, *Atti R. Accad. Lincei*, 1906, **15**, ii, 555.

known [14,30] and it has been found to proceed with Δ^1-pyrrolines in which the 2-position is unsubstituted: for example, 5 : 5-dimethyl-Δ^1-pyrroline readily gave 5-cyano-2 : 2-dimethylpyrrolidine (VII; R = Me) which was reduced by lithium aluminium hydride to the corresponding diamine and hydrolysed with hydrochloric acid to 5 : 5-dimethylproline (VIII; R = Me).



(IIIa) (VII) (VIII)

A similar series of reactions was performed with 4 : 5 : 5-trimethyl-Δ^1-pyrroline although the separation of the various diastereoisomers was not attempted. The formulation of the products follows from the analyses of the nitriles, the prolines, and the salts of the diamines, together with the electrometric titration of the latter.[31]

The addition of hydrogen cyanide to Δ^1-pyrrolines thus provides a novel and convenient route to various substituted prolines, some of which occur naturally.[32] Proline, too, can be made by this method, for on treatment of 4-amino-1 : 1-diethoxybutane with hydrochloric acid and potassium cyanide the amino-nitrile (VII; R = H) was obtained: subsequent hydrolysis then gave proline (VIII; R = H).

Experimental

The organic bases were isolated by adjusting their aqueous solutions to pH 11 with aqueous potassium hydroxide and extracting these solutions continuously with ether for several hours. Drying ($MgSO_4$) of the extract followed. Unless otherwise stated, the picrates were yellow, were prepared in moist ether, and were recrystallised from ethanol or propan-1-ol. Infrared spectra were measured by using Nujol or hexachlorobutadiene mulls or liquid films.

Preparation of Δ^1-Pyrrolines from γ-Nitro-carbonyl Compounds (with Drs. R. F. C. Brown and M. Lamchen).—(a) *5 : 5-Dimethyl-Δ^1-pyrroline.* 4-Methyl-4-nitropentan-1-al (70 g.; prepared by condensation of 2-nitropropane and acraldehyde in presence of sodium methoxide [33]), dry ethylene glycol (35 g.), and toluene-*p*-sulphonic acid (1 g.) were heated under reflux in benzene (200 ml.), the water produced (9 ml.) being retained in a Dean–Stark trap. The benzene solution was washed with aqueous sodium hydrogen carbonate, dried, and fractionated to give *2-(3-methyl-3-nitrobutyl)-1 : 3-dioxolan* (68 g., 75%), b. p. 105°/0·5 mm. (Found: C, 51·0; H, 8·2; N, 7·35. $C_8H_{15}O_4N$ requires C, 50·8; H, 8·0; N, 7·4%). The dioxolan (63 g.) was hydrogenated in methanol (30 ml.) over Raney nickel (5 g.) at room temperature and 115 atm. for 20 hr., the catalyst removed, solvent evaporated, and the residue heated under reflux with 7·5N-hydrochloric acid (65 ml.) for 20 min. The cooled solution was made alkaline with aqueous potassium hydroxide and extracted with ether. Fractionation of the dried extract gave *5 : 5-dimethyl-Δ^1-pyrroline*, b. p. 104—108° (17 g., 53%), whose infrared spectrum showed peaks at 1621, 1378, and 1361 cm.$^{-1}$. The *hydrochloride*, a hygroscopic solid, exhibited a band at 1655 cm.$^{-1}$. The *picrate* crystallised as yellow prisms (from ethanol–ether), m. p. 120—124° (Found: C, 44·5; H, 4·6; N, 17·1. $C_{12}H_{14}O_7N_4$ requires C, 44·2; H, 4·3; N, 17·2%).

(b) *4 : 5 : 5-Trimethyl-Δ^1-pyrroline.* 3 : 4-Dimethyl-4-nitropentan-1-al, prepared according to Warner and Moe's instructions,[33] was converted in 63% yield into the *1 : 3-dioxolan*, b. p. 100°/0·4 mm. (Found: C, 53·5; H, 8·2; N, 7·1. $C_9H_{17}O_4N$ requires C, 53·2; H, 8·4; N, 7·0%). The dioxolan was hydrogenated and hydrolysed, yielding *4 : 5 : 5-trimethyl-Δ^1-pyrroline*, b. p. 127—130°, in 61% yield (Found: C, 75·2; H, 12·3; N, 12·9. $C_7H_{13}N$ requires C, 75·6; H, 11·8; N, 12·6%). The infrared band of C=N was at 1617 cm.$^{-1}$. The *picrate* formed prisms, m. p. 173° (Found: C, 46·0; H, 4·8; N, 16·6. $C_{13}H_{16}O_7N_4$ requires C, 45·9; H, 4·7; N, 16·5%).

[30] Dornow and Lüpfert, *Chem. Ber.*, 1956, **89**, 2718.
[31] Rometsch, Marxer, and Miescher, *Helv. Chim. Acta*, 1951, **34**, 1611.
[32] Hulme and Arthington, *Nature*, 1954, **174**, 588; Hulme, *ibid.*, 1055; Kenner and Sheppard, *ibid.*, 1958, **181**, 48.
[33] Shechter, Ley, and Zeldin, *J. Amer. Chem. Soc.*, 1952, **74**, 3664; Warner and Moe, *ibid.*, p. 1064.

(c) 2 : 4 : 4-*Trimethyl*-Δ^1-*pyrroline*. 4 : 4-Dimethyl-5-nitropentan-2-one[34] was converted into the corresponding *dioxolan*, b. p. 90°/0·7 mm. (81%) (Found: C, 53·0; H, 8·2; N, 6·9. $C_9H_{17}O_4N$ requires C, 53·2; H, 8·4; N, 7·0%), from which 2 : 4 : 4-*trimethyl*-Δ^1-*pyrroline*, b. p. 126—129°, was prepared in 38% yield. The infrared band of the C=N group was at 1644 cm.$^{-1}$. The *picrate*, needles, m. p. 195°, exhibited a band at 1684 cm.$^{-1}$ (Found: C, 45·8; H, 4·9; N, 16·5. $C_{13}H_{16}O_7N_4$ requires C, 45·9; H, 4·7; N, 16·5%).

Preparation of Pyrrolidines.—(a) 2-*Methylpyrrolidine*. Lævulic acid oxime[35] (50 g.) in methanol (200 ml.) was hydrogenated over Raney nickel (8 g.) in an autoclave at 100°/100 atm. for 2 hr.; after removal of the catalyst, fractionation gave 5-methylpyrrolid-2-one (26 g., 69%), b. p. 135—143°/15 mm. Reduction of this with lithium aluminium hydride[36] yielded 2-methylpyrrolidine (65%), b. p. 92—93°, whose chloroplatinate[37] formed orange needles, m. p. 208°, from aqueous ethanol. Picric acid gave a *picrate–picric acid complex* as orange prisms, m. p. 89°, after recrystallisation from ethanol (Found: C, 37·6, 37·9; H, 3·1, 3·1; N, 18·3, 18·0; equiv., 566, 553. $C_5H_{11}N,2C_6H_3O_7N_3$ requires C, 37·6; H, 3·15; N, 18·1%; equiv., 543. $C_5H_{11}N,C_6H_3O_7N_3$ requires C, 42·2; H, 4·2; N, 17·9%; equiv., 314). This compound is probably identical with that reported[38] as the picrate, m. p. 88·5—89·5°, for which only a nitrogen analysis (N, 17·84%) was given.

(b) 2 : 5-*Dimethylpyrrolidine*. The mixture of Δ^1- and Δ^3-pyrrolines from the reduction of 2 : 5-dimethylpyrrole with zinc and hydrochloric acid was catalytically hydrogenated over platinum oxide to give 2 : 5-dimethylpyrrolidine, b. p. 101—109°, whose picrate formed yellow needles, m. p. 120°. Evans[4] records m. p. 120—121° for the picrate of the *cis*-isomer.

(c) 2 : 2-*Dimethylpyrrolidine*. (i) 5 : 5-Dimethyl-Δ^1-pyrroline (3 g.) was heated under reflux in 6N-hydrochloric acid (40 ml.) with granulated tin (15 g.) for 5 hr. The solution was then made strongly alkaline with aqueous potassium hydroxide and steam-distilled. Ether-extraction of the distillate followed by fractionation of the dried extract gave 2 : 2-dimethylpyrrolidine (0·87 g., 29%), b. p. 102—105°. The picrate[39] formed yellow needles, m. p. 189° after recrystallisation from ethanol.

(ii) To a stirred slurry of lithium aluminium hydride (2 g.) in dry ether (25 ml.) at 0° a solution of 5 : 5-dimethyl-Δ^1-pyrroline (3 g.) in dry ether (25 ml.) was slowly added. The mixture was stirred for 30 min. and then heated under reflux for 3 hr. Excess of hydride was decomposed with saturated aqueous potassium carbonate, and the ether layer separated, washed, dried, and fractionated to give 1·85 g. (60%) of 2 : 2-dimethylpyrrolidine, b. p. 103—106°; the picrate had m. p. 188—189° undepressed on admixture with the specimen prepared as under (i) above.

(d) 2 : 2 : 3-*Trimethylpyrrolidine*. 4 : 5 : 5-Trimethyl-Δ^1-pyrroline was similarly reduced with tin and hydrochloric acid to 2 : 2 : 3-trimethylpyrrolidine (65%), b. p. 128—132°. The *picrate*, yellow needles from ethanol, had m. p. 221° (Found: C, 45·8; H, 5·1; N, 16·5. $C_{13}H_{18}O_7N_4$ requires C, 45·6; H, 5·3; N, 16·4%).

(e) 2 : 4 : 4-*Trimethylpyrrolidine*. (i) Reduction of 2 : 4 : 4-trimethyl-Δ^1-pyrroline by lithium aluminium hydride gave 2 : 4 : 4-*trimethylpyrrolidine*, b. p. 120—124°, in 50% yield. The *picrate* formed yellow prisms, m. p. 162—163°, from ethanol (Found: C, 45·6; H, 5·1; N, 16·6. $C_{13}H_{18}O_7N_4$ requires C, 45·6; H, 5·3; N, 16·4%).

(ii) Reduction of 2 : 4 : 4-trimethyl-Δ^1-pyrroline by tin and hydrochloric acid was slow. After 5 hr., gas chromatography indicated 60% conversion into the pyrrolidine and even after 18 hr. 10% of the pyrroline appeared unreduced.

Dehydrogenation of Pyrrolidines to Δ^1-*Pyrrolines* (cf. ref. 14).—The pyrrolidine (2—5 g.) and mercuric acetate (4 mol.) were heated under reflux in 10% aqueous acetic acid (100 ml.) for 20 hr. Mercurous acetate (sometimes accompanied by free mercury) slowly separated. After removal of the precipitate the filtrate was treated with hydrogen sulphide, again filtered, and excess of hydrogen sulphide removed under reduced pressure. The bases were extracted in the usual way, and a portion of the dried extract examined by gas chromatography (see below). Addition of a moist ethereal solution of picric acid to the bulk of the dried extract gave the

[34] Kloetzel, *J. Amer. Chem. Soc.*, 1947, **69**, 2270.
[35] Müller, *Ber.*, 1883, **16**, 1618.
[36] Cf. Karrer and Erhardt, *Helv. Chim. Acta*, 1951, **34**, 2209.
[37] Fenner and Tafel, *Ber.*, 1898, **31**, 906.
[38] Terentiev and Votadina, *Doklady Akad. Nauk S.S.S.R.*, 1953, **88**, 845.
[39] Cf. Buckley and Elliott, *J.*, 1947, 1508.

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pyrroline picrate, the pyrrolidine salts usually remaining in solution. The successful dehydrogenations are summarised in the Table.

Dehydrogenation of cyclic secondary amines.

			Δ¹-Pyrroline		
Pyrrolidine	Picrate, m. p.	Yield (%)	pK_a [b]	Picrate, m. p.	Infrared band of C=NH⁺ (cm.⁻¹)
2-Methyl	89° [a]	25	7·7	121°	1679
2 : 5-Dimethyl	121	30	8·0	135	1673
2 : 4 : 4-Trimethyl	162	47	7·6	195	1684

[a] (1 : 1) Picrate–picric acid complex. [b] Apparent pH recorded at 20° by a Pye glass electrode and meter for a 30% aqueous ethanol solution at the half-neutralisation point. The meter was standardised with aqueous buffer at pH 7.

Although a copious precipitate of mercurous acetate was formed, no low-boiling product was isolable when pyrrolidine itself was investigated. The reaction did not appear to proceed easily with 2 : 2-di- or 2 : 2 : 3-tri-methylpyrrolidine, little or no mercurous acetate being precipitated.

Attempted Addition of Various Nucleophilic Reagents to Δ¹-Pyrrolines.—(a) *Nitroalkanes.* No product was isolated from the interaction of 5 : 5-dimethyl-Δ¹-pyrroline with (i) nitroethane in the presence of sodium methoxide or (ii) nitromethane in the presence of the ion-exchange resin Dowex-2 (hydroxide form).

(b) *Ethylmagnesium bromide.* (i) To a stirred ethereal solution of ethylmagnesium bromide (from 7 g. of ethyl bromide) 5 : 5-dimethyl-Δ¹-pyrroline (4 g.) in dry ether (20 ml.) was added. The mixture rapidly became viscous; after being heated under reflux for 1½ hr. the solution was cooled and 6N-hydrochloric acid (30 ml.) added. Two hours later the mixture was made alkaline with potassium hydroxide and extracted with ether. Fractionation of the extract furnished a viscous liquid (0·9 g.), b. p. 90°/0·5 mm., showing two basic groups, pK_{a_1} 5·4, pK_{a_2} 9·9 on electrometric titration. Further attempts at purification met with no success.

(ii) From an attempt to add ethylmagnesium bromide to 2 : 4 : 4-trimethyl-Δ¹-pyrroline 40% of the starting material was recovered and only a trace of high-boiling material was formed.

Addition of Hydrogen Cyanide to Δ¹-Pyrrolines.—(i) *5-Cyano-2 : 2-dimethylpyrrolidine.* To a stirred solution of potassium cyanide (4·5 g.) and 5 : 5-dimethyl-Δ¹-pyrroline (5 g.) in water (20 ml.) at 0° 2N-hydrochloric acid (50 ml.) was added during 2 hr. The mixture (which had pH 6) was left at room temperature overnight, then made alkaline with potassium hydroxide and extracted with ether. Fractionation of the dried extract gave *5-cyano-2 : 2-dimethylpyrrolidine* (2·84 g., 44%), b. p. 164—166° (Found: C, 67·5; H, 10·0; N, 22·5. $C_7H_{12}N_2$ requires C, 67·7; H, 9·7; N, 22·6%). The infrared spectrum (liquid film) showed peaks at 3310, 2245, 1385, and 1368 cm.⁻¹.

Reduction of the nitrile in ether by lithium aluminium hydride gave 5-aminomethyl-2 : 2-dimethylpyrrolidine isolated as the *dipicrate*, yellow needles, m. p. 225° (decomp.) after recrystallisation from ethanol (Found: C, 39·0; H, 4·05; N, 19·3. $C_{19}H_{22}O_{14}N_8$ requires C, 38·9; H, 3·8; N, 19·1%).

(ii) *5-Cyano-2 : 2 : 3-trimethylpyrrolidine.* Addition of hydrogen cyanide to 4 : 5 : 5-trimethyl-Δ¹-pyrroline furnished *5-cyano-2 : 2 : 3-trimethylpyrrolidine* (48%), b. p. 178—180°, presumably as a mixture of diastereoisomers (Found: C, 69·5; H, 10·8; N, 19·4. $C_8H_{14}N_2$ requires C, 69·5; H, 10·2; N, 20·3%). The infrared spectrum (liquid film) showed max. at 3320 and 2240 cm.⁻¹. Reduction of this nitrile with lithium aluminium hydride yielded *5-aminomethyl-2 : 2 : 3-trimethylpyrrolidine* (42%), b. p. 192—196°, pK_{a_1} 6·8, pK_{a_2} 10·5 (cf. ref. 31); the *diperchlorate* formed prisms, m. p. 250—254° (decomp.) after recrystallisation from ethanol–ether (Found: C, 28·1; H, 6·0; N, 8·0. $C_8H_{20}O_8N_2Cl_2$ requires C, 28·0; H, 5·9; N, 8·2%). The dipicrate could not be recrystallised to constant m. p.

(iii) Attempted addition of hydrogen cyanide to 2 : 4 : 4-trimethyl-Δ¹-pyrroline led only to a 63% recovery of the starting material.

Preparation of Prolines.—(a) *5 : 5-Dimethylproline.* 5-Cyano-2 : 2-dimethylpyrrolidine (0·95 g.) in 6N-hydrochloric acid (20 ml.) was heated under reflux for 6 hr. Evaporation to dryness under reduced pressure gave a residue which was dissolved in water (10 ml.) and percolated through a column (10 cm. × 1·5 cm.²) of Dowex-1 resin (acetate form). The residue obtained

on evaporation of the eluate was dried *in vacuo* at 90° for 2 hr., and then recrystallised from ethanol–ether (charcoal) to give 5 : 5-*dimethylproline* (0·81 g., 74%) as needles, m. p. 190—195°, raised to 194—196° on further recrystallisation (Found: C, 58·5; H, 9·4; N, 9·8. $C_7H_{13}O_2N$ requires C, 58·7; H, 9·15; N, 9·8%). The infrared spectrum (mull) of the freshly dried material showed maxima at 3420, 3100, 2725, 1620, and 1580 cm.$^{-1}$; on exposure of the material to the atmosphere for 30 min. the maxima moved to 3440, 3360, 3245, 3135, 2725, 2420, 1684, and 1609 cm.$^{-1}$. In paper chromatography, butan-1-ol–acetic acid–water (4 : 1 : 5, upper phase) gave R_F 0·52; phenol saturated with water (hydrogen cyanide atmosphere) gave R_F 0·87. The amino-acid gave no colour on paper when sprayed with isatin; with ninhydrin a purple-brown colour slowly developed during 30 min. at 90°. In alkaline solution, 5 : 5-dimethylproline gave a blue colour with acetaldehyde and sodium nitroprusside.[40]

(b) 4 : 5 : 5-*Trimethylproline*. Hydrolysis of 5-cyano-2 : 2 : 3-trimethylpyrrolidine yielded 4 : 5 : 5-*trimethylproline* (mixture of diastereoisomers?) as rosettes, m. p. 226—228° (from ethanol–ether) (Found: C, 60·8; H, 10·1; N, 8·75. $C_8H_{15}O_2N$ requires C, 61·1; H, 9·6; N, 8·9%). The infrared spectrum had maxima at 3400, 2710, 2465, and 1620 cm.$^{-1}$. On paper chromatography, the R_F value in the butanol system (above) was 0·61; in the phenol system (above) 0·86. Colour reactions with various reagents were similar to those of 5 : 5-dimethylproline.

(c) *Proline*. 2N-Hydrochloric acid (25 ml.) was slowly added at 0° to a stirred mixture of 4-amino-1 : 1-diethoxybutane [41] (3 g.) and potassium cyanide (1·8 g.) in water (15 ml.). The final pH was 2. The mixture was left at room temperature overnight and then a further addition of 2N-hydrochloric acid (10 ml.) was made and the solution warmed to 50° for 20 min. After cooling, the solution was made alkaline with potassium hydroxide solution and extracted with ether. Fractionation of the dried extract gave crude 2-*cyanopyrrolidine* (0·55 g., 29%), b. p. 168—172°. The infrared spectrum (liquid film) had maxima at 3340 and 2250 cm.$^{-1}$; electrometric titration gave an equivalent of 104 (theory, 96). The nitrile was hydrolysed in the usual way to yield proline (69%) as needles, m. p. 208—210° (from ethanol) (Found: C, 52·3; H, 8·0; N, 12·05. Calc. for $C_5H_9O_2N$: C, 52·2; H, 7·9; N, 12·2%). The infrared spectrum of the dry material showed maxima at 3170, 2715, 2402, and 1613 cm.$^{-1}$: after 2 hr. in moist air the maxima appeared at 3500, 3350, 3180, 2710, 2402, 1645, 1609, and 1589 cm.$^{-1}$. Identical values were observed on using an authentic sample of proline. Paper chromatography in the butanol system (above) gave R_F 0·35; and in the phenol system (above) R_F 0·83.

Gas Chromatography of Pyrrolidines and Δ^1-*Pyrrolines*.—Chromatograms were obtained by using a Perkin–Elmer vapour fractometer (Model 154), the column (200 cm. × 0·12 cm.^{2}) being packed with polyethylene glycol (average mol. wt. 400) (1 part) on Silocell (60—70 mesh) (5 parts).

Samples (*ca.* 0·01 ml. of liquid) were applied with nitrogen as the carrier gas at an excess pressure of 12·2 lb./sq. in. At 97°, the uncorrected retention volumes (ml.) were: pyrrolidine, 36; 2-methylpyrrolidine, 34; 2-methyl-Δ^1-pyrroline, 55; 2 : 5-dimethylpyrrolidine, 32; 2 : 5-dimethyl-Δ^1-pyrroline, 60; 2 : 4 : 4-trimethylpyrrolidine, 38; 2 : 4 : 4-trimethyl-Δ^1-pyrroline, 66; 5 : 5-dimethylpyrrolidine, 32; 5 : 5-dimethyl-Δ^1-pyrroline, 34; 2 : 2 : 3-trimethylpyrrolidine, 55; 4 : 5 : 5-trimethyl-Δ^1-pyrroline, 60; ether, 4; acetone, 8·5; benzene, 15; methanol, 17; ethanol, 17; water, 45.

We are grateful to Dr. J. H. Purnell for advice on gas chromatography, to the Salters' Company for the award of a Fellowship (to R. B.), and to the Swiss " Stiftung für Stipendien auf dem Gebiete der Chemie " for a grant (to A. G.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, January 20th*, 1959.]

[40] Cf. Feigl, " Spot Tests. II. Organic Applications," Elsevier, Amsterdam, 1954, p. 189.
[41] *Org. Synth.*, 1931, **11**, 26; Manske, *Canad. J. Res.*, 1931, **5**, 592.

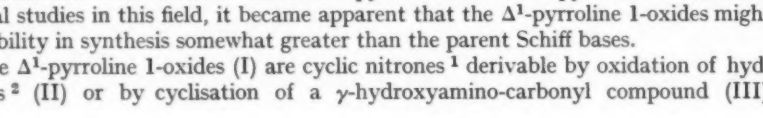
423. *Experiments towards the Synthesis of Corrins. Part II.* The Preparation and Reactions of Δ^1-Pyrroline 1-Oxides.*

By R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and Sir Alexander Todd.

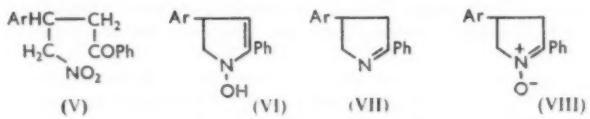
The reduction of γ-nitro-carbonyl compounds to give Δ^1-pyrroline 1-oxides is described and the reactions of several such *N*-oxides are reported.

The corrin nucleus, parent of the macrocyclic component of the vitamin B_{12} molecule, is at an oxidation level between that of the pyrroles and the Δ^1-pyrrolines and, in our synthetical studies in this field, it became apparent that the Δ^1-pyrroline 1-oxides might offer a flexibility in synthesis somewhat greater than the parent Schiff bases.

The Δ^1-pyrroline 1-oxides (I) are cyclic nitrones [1] derivable by oxidation of hydroxylamines [2] (II) or by cyclisation of a γ-hydroxyamino-carbonyl compound (III). As



γ-nitro-aldehydes and ketones (IV) are readily available the generation of Δ^1-pyrroline 1-oxides depends upon the reduction of the nitro- to the hydroxyamino-group. Kohler and Drake in their early work [3] upon the catalytic hydrogenation of 3-(3 : 4-methylenedioxyphenyl)-4-nitro-1-phenylbutan-1-one (V) obtained an oxygenated product to which they assigned the hydroxylated pyrroline structure (VI). Recently, Kloetzel and Pinkus [4] have repeated this work and, using zinc dust and aqueous ammonium chloride, have



Ar = 3 : 4-methylenedioxyphenyl

obtained the pyrroline (VII), but no trace of (VI). In our hands, the zinc dust method has given Kohler and Drake's oxygenated product, to which we now assign the Δ^1-pyrroline 1-oxide formulation (VIII).

The use of zinc dust in cold aqueous ammonium chloride has proved of general utility in the reduction of γ-nitro-carbonyl compounds to the Δ^1-pyrroline 1-oxides though, on occasion, the carbonyl function has to be protected as an acetal. Thus, reduction of 4 : 4-dimethyl-5-nitropentan-2-one [5] (IV; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$) gave 2 : 4 : 4-trimethyl-Δ^1-pyrroline 1-oxide (I; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$) in 75% yield, and 3 : 4-dimethyl-4-nitropentanal gave 51% of the 4 : 5 : 5-trimethylpyrroline oxide. 4-Methyl-4-nitropentanal (IV; $R^3 = R^4 = R^5 = H$; $R^1 = R^2 = Me$), however, gave only a low yield of the pyrroline 1-oxide, and the required 5 : 5-dimethyl-Δ^1-pyrroline 1-oxide (I; $R^3 = R^4 = R^5 = H$; $R^1 = R^2 = Me$) was subsequently obtained by reduction of the nitro-aldehyde diethyl acetal to the corresponding hydroxylamine followed by hydrolysis

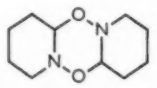
* Part I, preceding paper.

[1] Smith, *Chem. Rev.*, 1938, **23**, 193.
[2] Cf. Rupe and Wittwer, *Helv. Chim. Acta*, 1922, **5**, 217; Utzinger, *Annalen*, 1944, **556**, 50; Thesing, *Chem. Ber.*, 1954, **87**, 507.
[3] Kohler and Drake, *J. Amer. Chem. Soc.*, 1923, **45**, 2144.
[4] Kloetzel and Pinkus, *ibid.*, 1958, **80**, 2332.
[5] Kloetzel, *ibid.*, 1947, **69**, 2271.

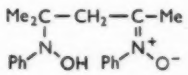
of the protecting acetal group. 5-Ethoxycarbonyl-5-methyl-Δ^1-pyrroline 1-oxide was prepared from the ethylene acetal of 4-ethoxycarbonyl-4-nitropentanal by a similar method.

The *N*-oxides were extremely hygroscopic oils whose satisfactory analysis proved difficult but, being weakly basic, they were readily characterised as picrates. Each showed a single ultraviolet absorption maximum, at 229—235 mμ (ε ~9000), attributable to the $>C=^{+}N-O^{-}$ chromophore. This group exhibited strong infrared absorption, the frequency ranging from 1600 to 1620 cm.$^{-1}$ for those compounds bearing a 2-alkyl substituent and from 1570 to 1590 cm.$^{-1}$ when no such substituent was present (*i.e.*, I; $R^5 = H$).

These Δ^1-pyrroline 1-oxides are the first monomeric non-aromatic nitrones to be reported,[6] their formation being closely parallel to that of the amino-Δ^1-pyrroline 1-oxide (I; $R^1 = R^2 = Me$, $R^3 = R^4 = H$, $R^5 = NH_2$) resulting from the reduction of 3-methyl-3-nitrobutyl cyanide.[7] The aliphatic and alicyclic nitrones so far reported have generally been obtained as dimers; thus, oxidation of 1-hydroxypiperidine does not give the expected cyclic nitrone but a product to which the dimeric structure (IX) has been assigned.[8] In other cases aldol-type dimers are formed; acetone and phenylhydroxylamine give the dimer (X),[9] and the condensation product of *n*-butyraldehyde and phenylhydroxylamine has been reported [10] to be of the same type. The condensation product of formaldehyde and phenylhydroxylamine dimerises in yet another manner [11] which will be considered in a subsequent paper.



(IX)



(X)

The ease of preparation of the Δ^1-pyrroline 1-oxides and their relative stability has afforded an opportunity to examine their reactions in some detail. The analogy between the $>C=^{+}N-O^{-}$ group and the carbonyl group is striking and well known in the aryl-substituted nitrones where addition of nucleophilic reagents, *e.g.*, phenylhydrazine or semicarbazide, has often led to a derivative of the parent carbonyl compound with loss of the hydroxyamino-residue.[12] With the Δ^1-pyrroline 1-oxides addition of cyanide ion, a Grignard reagent, or the anion of a nitroalkane proceeds smoothly; moreover, activation of an α-methyl group (*e.g.*, in the condensation with an aldehyde under basic conditions) is readily observed. Reactions depending on the back-polarisation of the system $>C=^{+}N-O^{-} \longleftrightarrow >C^{-}-^{+}N=O$ will be discussed in a later paper.

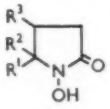
Δ^1-Pyrroline 1-oxides (I) were readily reduced to the cyclic secondary hydroxylamines (II) by aqueous potassium borohydride. These hydroxylamines, on treatment with toluene-*p*-sulphonyl chloride and triethylamine in ether, afforded Δ^1-pyrrolines in moderate yield (30—40%), presumably through the elimination of toluene-*p*-sulphonic acid from an intermediate *O*-toluene-*p*-sulphonyl compound in a manner analogous to that by which Schöpf obtained Δ^1-piperideine derivatives from 1-chloropiperidine.[13] In the examples studied the direction of elimination followed the Saytzeff rule. Reduction of (I; $R^1 = R^2 = H$; $R^3 = R^4 = R^5 = Me$) by zinc and acetic acid gave the pyrroline, but tin and hydrochloric acid brought about further reduction to the pyrrolidine. Treating a Δ^1-pyrroline 1-oxide with a solution of sulphur dioxide in chloroform also gave a small yield of the pyrroline.

[6] Brown, Clark, and Todd, *Proc. Chem. Soc.*, 1957, 97.
[7] Buckley and Elliott, *J.*, 1947, 1508.
[8] Thesing and Mayer, *Chem. Ber.*, 1956, **89**, 2159.
[9] Banfield and Kenyon, *J.*, 1926, 1612.
[10] Utzinger and Regenass, *Helv. Chim. Acta*, 1954, **37**, 1892.
[11] Bamberger, *Ber.*, 1900, **33**, 941; Hellmann and Teichmann, *Chem. Ber.*, 1956, **89**, 1134.
[12] Staudinger and Miescher, *Helv. Chim. Acta*, 1919, **2**, 554; Kröhnke and Börner, *Ber.*, 1936, **69**, 2006.
[13] Schöpf, Komak, Braun, and Jacobi, *Annalen*, 1948, **559**, 1.

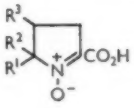
XUM

Addition of Grignard reagents to nitrones [14] proceeds smoothly with the dimeric tetrahydropyridine 1-oxide (IX), and the Δ^1-pyrroline 1-oxides (I; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$; and $R^1 = R^2 = Me$, $R^3 = R^4 = R^5 = H$) behaved similarly, giving the 2-alkyl cyclic hydroxylamines in high yield. Copper-catalysed aerial oxidation in alkaline solution [15] converted these 1-hydroxypyrrolidines into Δ^1-pyrroline 1-oxides once again. Re-oxidation, under these conditions, of the cyclic hydroxylamine (II; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$) gave the pyrroline oxide (I; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$), *i.e.*, the product with the more highly substituted nitrone grouping was formed.

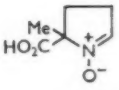
Those Δ^1-pyrroline 1-oxides unsubstituted at position 2, *i.e.*, where $R^5 = H$, with hydrogen cyanide in aqueous solution gave 2-cyano-1-hydroxypyrrolidines, analogous to cyanohydrins. The cyano-hydroxypyrrolidines (II; $R^1 = R^2 = Me$, $R^3 = R^4 = H$, $R^5 = CN$; and $R^1 = R^2 = R^3 = Me$, $R^4 = H$, $R^5 = CN$) underwent copper-catalysed aerial oxidation in alkaline solution to the 2-cyano-Δ^1-pyrroline 1-oxides which, on alkaline hydrolysis, gave the expected 2-carboxylic acids together with the cyclic hydroxamic acids (XI). The latter presumably arise through replacement of cyanide by hydroxyl as in the alkaline hydrolysis of acyl cyanides. The structure of the cyclic hydroxamic acid (XI; $R^1 = R^2 = Me$, $R^3 = H$) was confirmed by its synthesis from methyl 4-methyl-4-nitropentanoate by reduction with zinc in ammonium chloride solution.



(XI)



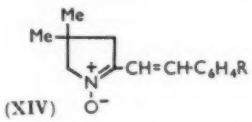
(XII)



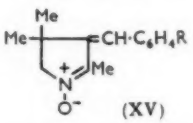
(XIII)

The 2-carboxy-Δ^1-pyrroline 1-oxides (XII; $R^1 = R^2 = Me$, $R^3 = H$; and $R^1 = R^2 = R^3 = Me$) were decarboxylated above 140° to the pyrroline oxides; the 5-carboxylic acid (XIII) decomposed at the same temperature but gave no identifiable product.

Base-catalysed addition of nitroalkanes to a carbonyl group yields β-nitro-alcohols: as expected, addition of nitromethane and nitroethane to a Δ^1-pyrroline 1-oxide gave the β-nitro-hydroxylamines. However, the pyrroline oxides themselves can yield carbanions in the presence of bases (cf. ref. 10), and the oxide (I; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$) underwent base-catalysed condensation with benzaldehyde and *p*-nitrobenzaldehyde to give crystalline monobenzylidene derivatives. Of the possible structures (XIV) and (XV), formulation (XIV) is preferred since the infrared spectrum of the benzylidene



(XIV)



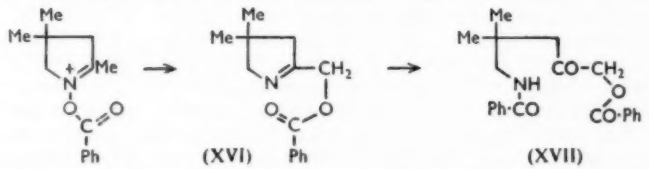
(XV)

derivative (R = H) showed a strong band at 977 cm.$^{-1}$ indicative of a *trans*-disubstituted ethylene rather than a trisubstituted ethylene.[16] Furthermore, Δ^1-pyrroline 1-oxides having no 2-methyl group failed to condense with *p*-nitrobenzaldehyde under the same conditions; and so did the ethyl analogue (I; $R^1 = R^2 = Me$, $R^3 = R^4 = H$, $R^5 = Et$).

Although nitrones give addition products with phenyl *iso*cyanate [12,17] and are weakly basic, attempted acylation of the Δ^1-pyrroline 1-oxides leads to rearrangement. Benzoylation of the oxide (I; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$) under Schotten–Baumann conditions gave a crystalline product, $C_{21}H_{23}O_4N$, containing two benzoyl residues and a

[14] Angeli, Alessandri, and Aiazzi-Mancini, *Atti R. Accad. Lincei*, 1911, **20**, i, 546.
[15] Johnson, Rogers, and Trappe, *J.*, 1956, 1093.
[16] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, Second Edition, 1958, p. 45.
[17] Goldschmidt and Kjellin, *Ber.*, 1891, **24**, 2808.

carbonyl group which readily gave rise to a 2 : 4-dinitrophenylhydrazone. The presence of strong bands at 3360, 1637, and 1547 cm.$^{-1}$ in the infrared spectrum showed that one benzoyl group was present in a secondary amide, and a strong band at 1718 cm.$^{-1}$ could be assigned to the carbonyl group of a benzoate or an aliphatic carbonyl group or both. On this evidence we assign structure (XVII) to the compound. Its formation involves an



acyl migration formally analogous to that in the formation of 2-benzoyloxymethylquinoline on benzoylation of quinaldine *N*-oxide.[18] In the present case the rearrangement probably proceeds through a cyclic transition state to give the intermediate pyrroline (XVI) which then undergoes ring-fission and benzoylation.

Experimental

2 : 4 : 4-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide*.—4 : 4-Dimethyl-5-nitropentan-2-one [5] (33·0 g.) and ammonium chloride (9 g.) in water (250 ml.) were stirred vigorously with ice-cooling whilst zinc dust (45 g.) was added during 2 hr. Stirring was continued for a further 2 hr., the mixture filtered, and the filter cake washed with warm water (4 × 50 ml.). The filtrate and washings were combined and evaporated below 60° to a thick syrup which was dissolved in chloroform (75 ml.). This solution was dried (Na_2SO_4) and evaporated and the residue distilled to give 2 : 4 : 4-*trimethyl*-Δ^1-*pyrroline* 1-*oxide* (19·8 g., 75%) as a colourless hygroscopic oil, b. p. 72°/0·4 mm. (Found: C, 64·8; H, 10·6. $C_7H_{13}ON$ requires C, 66·1; H, 10·3%), $\nu_{max.}$ (liquid film) 1613 cm.$^{-1}$, $\lambda_{max.}$ (in 95% ethanol) 229 mμ (ε 9000). The *picrate* formed lemon-yellow needles, m. p. 111°, from ethanol (Found: C, 44·0; H, 4·5; N, 15·3. $C_{13}H_{16}O_8N_4$ requires C, 43·8; H, 4·5; N, 15·7%). Dissolution of the nitrone in excess of methyl iodide gave, overnight, the *methiodide* as off-white, light-sensitive prisms, having m. p. 106° (decomp.) on recrystallisation from ethanol–ether (Found: C, 35·6; H, 5·8; N, 5·2. $C_8H_{16}ONI$ requires C, 35·7; H, 6·0; N, 5·2%).

4 : 5 : 5-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide*.—Freshly distilled crotonaldehyde (17·5 g.) in anhydrous methanol (25 ml.) was added dropwise to a solution of 2-nitropropane (25 g.) in anhydrous methanol (40 ml.) containing sodium methoxide (from 1 g. of sodium), the temperature being kept at 60°. After being stirred for 3 hr. the solution was left overnight. Acetic acid (3 ml.) was added, the methanol evaporated, and the residue poured into water. The product was extracted with ether, the extract washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated, and the residue distilled, yielding 3 : 4-*dimethyl*-4-*nitropentanal* (20·4 g., 51%), b. p. 80°/0·5 mm. (Found: C, 53·2; H, 8·2; N, 8·4. $C_7H_{13}O_3N$ requires C, 52·8; H, 8·2; N, 8·8%). Its *semicarbazone* formed leaflets, m. p. 150—151°, from aqueous ethanol (Found: C, 44·7; H, 7·3. $C_8H_{16}O_3N_4$ requires C, 44·4; H, 7·5%).

Reduction of this pentanal (60 g.) with zinc dust (74 g.) and ammonium chloride (15 g.) in water (400 ml.) gave 4 : 5 : 5-trimethyl-Δ^1-pyrroline 1-oxide (24·3 g., 51%), b. p. 85°/1 mm., $\lambda_{max.}$ 234 mμ (ε 8800) in 95% ethanol, $\nu_{max.}$ (liquid film) 1572 cm.$^{-1}$. The *picrate* formed lemon-yellow laths, m. p. 112°, from ethanol (Found: C, 44·1; H, 4·7; N, 15·4. $C_{13}H_{16}O_8N_4$ requires C, 43·8; H, 4·5; N, 15·7%).

5 : 5-*Dimethyl*-Δ^1-*pyrroline* 1-*Oxide*.—2-(3-Methyl-3-nitrobutyl)-1 : 3-dioxolan [19] (50 g.) and ammonium chloride (15 g.) in water (300 ml.) at 10° were rapidly stirred whilst zinc dust (70 g.) was added during 20 min., ice being introduced to keep the temperature below 15°. The mixture was stirred for 15 min., then filtered, and the filter cake washed with hot water (70°) (5 × 35 ml.). The combined filtrate and washings were acidified with concentrated hydrochloric acid (40 ml.), left overnight, and then heated to 75° for 1 hr. before being evaporated at >60° to 150 ml., made alkaline, and reduced in bulk to 100 ml. After saturation with borax

[18] Pachter, *J. Amer. Chem. Soc.*, 1953, **75**, 3026.
[19] Bonnett, Clark, Giddey, and Todd, preceding paper.

the solution was extracted with chloroform (6 × 75 ml.), and the extract dried (Na_2SO_4) and fractionated to yield 5 : 5-dimethyl-Δ^1-pyrroline 1-oxide (23·6 g., 79%), b. p. 66—67°/0·6 mm., hygroscopic, $\lambda_{max.}$ 234 mμ (ε 7700) in 95% ethanol, $\nu_{max.}$ (liquid film) 1573 cm.$^{-1}$. The *picrate* crystallised from ethanol in yellow needles, m. p. 81° (Found: C, 41·7; H, 4·2; N, 16·1%; equiv. of base, 115. $C_{12}H_{14}O_8N_4$ requires C, 42·1; H, 4·1; N, 16·4%; equiv. of base, 113). Reduction of 4-methyl-4-nitropentanal with zinc dust and ammonium chloride gave the pyrroline 1-oxide (27%) and a high-boiling residue.

4-(3 : 4-*Methylenedioxyphenyl*)-2-*phenyl*-Δ^1-*pyrroline* 1-*Oxide*.—3-(3 : 4-Methylenedioxyphenyl)-4-nitro-1-phenylbutan-1-one [3] (V) (3·13 g.) and ammonium chloride (0·50 g.) in 1 : 3 v/v aqueous tetrahydrofuran (40 ml.) were stirred vigorously whilst zinc dust (3·9 g., 6 g.-atoms) was added during 1 hr. at ≯5—10°. After filtration and washing with hot methanol (50 ml.) the combined filtrate and washings were evaporated to a gum which was distributed between 5N-hydrochloric acid and ether. The aqueous acid layer was made alkaline and extracted with methylene chloride (4 × 10 ml.). Adding ether to the extract afforded 4-(3 : 4-*methylenedioxyphenyl*)-2-*phenyl*-Δ^1-*pyrroline* 1-*oxide* as needles (1·12 g., 40%), m. p. 145° (corr.) after recrystallisation from methylene chloride–ether (Found: C, 73·6; H, 5·4; N, 5·1. $C_{17}H_{15}O_3N$ requires C, 72·6; H, 5·4; N, 5·0%), $\nu_{max.}$ (mull) 1613 cm.$^{-1}$ (aryl-conjugated nitrone).

Reduction of the pyrroline 1-oxide (300 mg.) with zinc dust (1·2 g.) and ammonium chloride (0·3 g.) in 60% aqueous methanol (30 ml.) at room temperature for 8 hr. gave 4-(3 : 4-methylenedioxyphenyl)-2-phenyl-Δ^1-pyrroline,[4] isolated as the hydrochloride (200 mg., 62%), m. p. 235—240° (decomp.). The $\rangle C{=}^{+}N{-}$ group in this product provided an infrared maximum at 1660 cm.$^{-1}$.

Ethyl 2-*Methyl*-2-*nitro*-5-*oxopentanoate*.—Acraldehyde (14 ml.) was added to a stirred solution of ethyl α-nitropropionate [20] (36 g.) in ethanol (200 ml.) containing sodium ethoxide (from 0·3 g. of sodium), and the mixture maintained at 40—50° for 3 hr. Acetic acid (1 ml.) was added, the solvent evaporated, and the product isolated by extraction with benzene. Distillation gave the *aldehydo-ester* (31·5 g., 65%), b. p. 107°/0·5 mm. (Found: C, 47·2; H, 6·5; N, 7·2. $C_8H_{13}O_5N$ requires C, 47·3; H, 6·5; N, 6·9%). The 2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 75—76°, from ethanol (Found: C, 43·7; H, 4·5; N, 18·3. $C_{14}H_{17}O_8N_5$ requires C, 43·9; H, 4·5; N, 18·3%). The 1 : 3-*dioxolan* was prepared in 78% yield from the nitro-aldehyde and ethylene glycol in the presence of toluene-*p*-sulphonic acid. Fractionation gave an oil, b. p. 121—125°/0·5 mm. (Found: C, 48·6; H, 6·7; N, 5·9. $C_{10}H_{17}O_6N$ requires C, 48·6; H, 6·9; N, 5·7%).

5-*Carboxy*-5-*methyl*-Δ^1-*pyrroline* 1-*Oxide*.—The above dioxolan (28·5 g.) was reduced with zinc dust (41·5 g.) in 50% aqueous ethanol (200 ml.) containing ammonium chloride (5·5 g.). After removal of the excess of zinc and zinc oxide, the solution was concentrated to 50 ml. and extracted with chloroform (4 × 50 ml.). Evaporation of the dried (Na_2SO_4) chloroform solution gave the crude *hydroxylamine* (26 g.); molecular distillation (140—155°/0·3 mm.) of a small sample gave a viscous oil (Found: C, 51·2; H, 8·2; N, 6·0. $C_{10}H_{19}O_5N$ requires C, 51·5; H, 8·2; N, 6·0%). The hydroxylamine (25·5 g.) was dissolved in 0·3N-hydrochloric acid (400 ml.) and left overnight at room temperature. After neutralisation with ammonia the aqueous solution was evaporated below 60° and the residue extracted with chloroform. Fractionation of the dried (Na_2SO_4) extract gave 5-*ethoxycarbonyl*-5-*methyl*-Δ^1-*pyrroline* 1-*oxide* (11·6 g., 60%), b. p. 120°/0·3 mm. (Found: C, 53·6; H, 8·2; N, 7·5. Calc. for $C_8H_{13}O_3N$: C, 56·1; H, 7·7; N, 8·2. $C_8H_{13}O_3N,\frac{1}{2}H_2O$ requires C, 53·3; H, 7·8; N, 7·8%), $\nu_{max.}$ (liquid film) 1740 and 1585 cm.$^{-1}$. Treatment of the pyrroline 1-oxide ester (2·13 g.) with 2·5% aqueous sodium hydroxide (20 ml.) at 100° for 1 hr. followed by passage of the solution through a column of Dowex 50 (H^+ form) and evaporation of the acidic eluate gave 5-*carboxy*-5-*methyl*-Δ^1-*pyrroline* 1-*oxide* (1·37 g., 77%) as needles, m. p. 135—136° (decomp.) (from chloroform) (Found: C, 50·4; H, 6·5; N, 10·0%; equiv., 141. $C_6H_9O_3N$ requires C, 50·3; H, 6·3; N, 9·8%; equiv., 143). Titration in aqueous solution indicated an apparent pK_a 2·95. $\lambda_{max.}$ in 95% ethanol was at 235—236 mμ (ε 7700).

Reduction of Δ^1-*Pyrroline* 1-*Oxides with Potassium Borohydride*.—(i) 1-*Hydroxy*-2 : 4 : 4-*trimethylpyrrolidine*. Potassium borohydride (0·4 g.) and 2 : 4 : 4-trimethyl-Δ^1-pyrroline 1-oxide (2·5 g.) in water (10 ml.) were kept at room temperature for 2 days, then saturated with potassium carbonate, and the product was extracted with ether. The dried (K_2CO_3) extract was evaporated and the residue fractionated to give the crude *hydroxylamine* (0·86 g.), b. p.

[20] Kornblum, Blackwood, and Powers, *J. Amer. Chem. Soc.*, 1957, **79**, 2507.

95—100°/25 mm. Addition of anhydrous oxalic acid in acetone gave the *hydrogen oxalate*, needles, m. p. 88° (from acetone–ether) (Found: C, 49·2; H, 7·5; N, 6·5. $C_9H_{17}O_5N$ requires C, 49·3; H, 7·8; N, 6·4%). Both the free base and the salt readily reduced aqueous alkaline triphenyltetrazolium chloride to the red formazan.[21]

The base (0·5 g.) in water (10 ml.) containing ammonia (1 ml.; *d* 0·880) and copper sulphate (5 mg.) was re-oxidised to the pyrroline 1-oxide by bubbling air through the solution for 2 hr. The nitrone, isolated as previously described, was treated with an excess of ethanolic picric acid to yield the picrate of 2 : 4 : 4-trimethyl-Δ^1-pyrroline 1-oxide as lemon-yellow needles, m. p. and mixed m. p. 111°.

(ii) *1-Hydroxy-2 : 2 : 3-trimethylpyrrolidine.* Reduction of 4 : 5 : 5-trimethyl-Δ^1-pyrroline 1-oxide (0·63 g.) with potassium borohydride (0·2 g.) in water (10 ml.) followed by isolation of the cyclic hydroxylamine as described above gave the crude base; addition of ethanolic hydrogen chloride gave *1-hydroxy-2 : 2 : 3-trimethylpyrrolidine hydrochloride* as prisms, m. p. 163° (from thanol–ether) (Found: C, 50·7; H, 9·6; N, 8·6%; equiv., 169. $C_7H_{16}ONCl$ requires C, 50·8; H, 9·7; N, 8·5%; equiv., 166). Titration in aqueous solution indicated an apparent pK_a 5·9. The base readily reduced aqueous alkaline triphenyltetrazolium chloride.

Other Reductions of Δ^1-Pyrroline 1-Oxides.—(a) *With zinc and acetic acid.* 2 : 4 : 4-Trimethyl-Δ^1-pyrroline 1-oxide (0·5 g.), zinc dust (5 g.), acetic acid (2 ml.), and water 8 ml.) were heated under reflux for 5 hr. after which more acetic acid (2 ml.) was added and heating continued for a further 20 hr. The solution was made alkaline with aqueous sodium hydroxide and steam-distilled. Neutralisation of the distillate with picric acid, evaporation to dryness below 60°, and recrystallisation of the residue from ethanol gave 2 : 4 : 4-trimethyl-Δ^1-pyrrolinium picrate (0·88 g., 66%) as yellow needles, m. p. 192—193°, undepressed in admixture with an authentic specimen.[19]

(b) *With sulphur dioxide.* In 12 hr. at room temperature in chloroform saturated with sulphur dioxide, 2 : 4 : 4-trimethyl-Δ^1-pyrroline 1-oxide was reduced to the corresponding pyrroline, isolated as its picrate, in 15% yield.

(c) *With tin and hydrochloric acid.* 2 : 4 : 4-Trimethyl-Δ^1-pyrroline 1-oxide (0·5 g.), granulated tin (4 g.), concentrated hydrochloric acid (5 ml.), and water (5 ml.) were heated under reflux for 20 hr. after which working up as in (a) gave 2 : 4 : 4-trimethyl-Δ^1-pyrrolinium picrate (0·13 g.), needles, m. p. 192° undepressed on admixture with an authentic specimen.[19] The picrate mother-liquors were treated with charcoal, filtered, and concentrated. On cooling, clusters of yellow needles of 2 : 4 : 4-trimethylpyrrolidinium picrate appeared (0·32 g.), m. p. 162° undepressed in admixture with an authentic specimen [19] (Found: C, 45·8; H, 5·7; N, 16·6. Calc. for $C_{13}H_{18}O_7N_4$: C, 45·6; H, 5·3; N, 16·4%).

Dehydration of 1-Hydroxypyrrolidines by Toluene-p-sulphonyl Chloride and Triethylamine.—(a) *2 : 4 : 4-Trimethyl-Δ^1-pyrroline.* 1-Hydroxy-2 : 4 : 4-trimethylpyrrolidine (0·63 g.) and toluene-*p*-sulphonyl chloride (0·92 g., 1 mol.) in anhydrous ether (10 ml.) were treated with triethylamine (0·98 g., 2 mols.) in ether (5 ml.) whereupon a white precipitate was formed. After being left overnight at room temperature the triethylammonium salts (1·7 g.) were filtered off and the filtrate was extracted with dilute hydrochloric acid. The acid extract was made alkaline with aqueous sodium hydroxide and saturated with potassium carbonate, and the amines were extracted with ether. Gas chromatography (cf. ref. 19) of a sample of this ethereal solution indicated that the main product was 2 : 4 : 4-trimethyl-Δ^1-pyrroline contaminated with a little triethylamine. Addition of excess of ethanolic picric acid gave the pyrrolinium picrate (0·55 g., 33%) as yellow needles, m. p. and mixed m. p. 192°.

(b) *4 : 5 : 5-Trimethyl-Δ^1-pyrroline.* 1-Hydroxy-2 : 2 : 3-trimethylpyrrolidine (1·10 g.) and toluene-*p*-sulphonyl chloride (1·55 g., 1 mol.) in anhydrous ether (15 ml.) were treated with triethylamine (1·64 g., 2 mols.) in ether (5 ml.), kept overnight, and worked up as in the preceding experiment, to give an ethereal solution of the crude bases. These were transferred to water by using dilute sulphuric acid followed by addition of barium carbonate and filtration. The aqueous solution (30 ml.) was applied to a column (10 cm. × 3 cm.^{2}) of Amberlite IRC-50 resin (ammonium form) and eluted with water (200 ml.). Neutralisation of the eluate with hydrochloric acid, evaporation to dryness, dissolution in aqueous sodium hydroxide, extraction with ether, and addition of ethanolic picric acid led to 4 : 5 : 5-trimethyl-Δ^1-pyrrolinium picrate (1·08 g., 31%), yellow prisms (from acetone–ether), m. p. and mixed m. p. 172° (cf. ref. 19) (Found: C, 45·9; H, 4·7. Calc. for $C_{13}H_{16}O_7N_4$: C, 45·9; H, 4·7%).

[21] Cf. Snow, *J.*, 1954, 2588.

XUM

Addition of Hydrogen Cyanide to Δ^1*-Pyrroline* 1*-Oxides.*—(a) 5*-Cyano*-1*-hydroxy*-2 : 2*-dimethylpyrrolidine.* 2N-Hydrochloric acid (25 ml.) was added during 1½ hr. to a stirred solution of 5 : 5-dimethyl-Δ^1-pyrroline 1-oxide (5·0 g.) and potassium cyanide (3·9 g.) in water (20 ml.) at 0°. A white solid was precipitated. After a further 2 hr. the mixture was brought to pH 11 and continuously extracted with ether. Addition of light petroleum (b. p. 40—60°) to the extract gave 2*-cyano*-1*-hydroxy*-5 : 5*-dimethylpyrrolidine* (4·8 g., 78%), prisms, m. p. 92° (from ether–light petroleum) (Found: C, 60·2; H, 8·9; N, 20·0. $C_7H_{12}ON_2$ requires C, 60·0; H, 8·6; N, 20·0%), $\nu_{max.}$ (mull) 3230 and 2240 cm.$^{-1}$.

The above cyano-hydroxylamine (8·1 g.) and copper acetate (1·5 g.) in 60% aqueous ethanol (100 ml.) containing ammonia (5 ml.; *d* 0·880) were aerated until a permanent blue colour was restored. Concentration to 30 ml., extraction with chloroform, and fractionation of the extract gave 2*-cyano*-5 : 5*-dimethyl*-Δ^1*-pyrroline* 1*-oxide* (5·8 g., 73%), b. p. 110°/0·5 mm. (Found: C, 60·8; H, 7·5; N, 20·1. $C_7H_{10}ON_2$ requires C, 60·9; H, 7·3; N, 20·3%), $\nu_{max.}$ (liquid film) 2220 and 1540 cm.$^{-1}$, $\lambda_{max.}$ (in 95% ethanol) 271 mμ (ε 10,700).

(b) 2*-Cyano*-1*-hydroxy*-4 : 5 : 5*-trimethylpyrrolidine.* Treatment of 4 : 5 : 5-trimethyl-Δ^1-pyrroline 1-oxide with hydrochloric acid and potassium cyanide as above yielded 2*-cyano*-1*-hydroxy*-4 : 5 : 5*-trimethylpyrrolidine* (66%), needles, m. p. 109° (from ether–light petroleum) (Found: C, 62·3; H, 9·3; N, 18·1. $C_8H_{14}ON_2$ requires C, 62·3; H, 9·1; N, 18·2%), $\nu_{max.}$ (mull) 3360, 3290, 2270, and 2240 cm.$^{-1}$. Copper-catalysed aerial oxidation gave 2*-cyano*-4 : 5 : 5*-trimethyl*-Δ^1*-pyrroline* 1*-oxide* (76%) as plates, m. p. 86—87°, from ethyl acetate–light petroleum (Found: C, 63·1; H, 7·8; N, 18·3. $C_8H_{12}ON_2$ requires C, 63·1; H, 8·0; N, 18·4%), $\nu_{max.}$ (mull) 2210 and 1528 cm.$^{-1}$, $\lambda_{max.}$ (in 95% ethanol) 273 mμ (ε 11,100).

(c) 5*-Cyano*-1*-hydroxy*-2*-methylpyrrolidine*-2*-carboxylic acid.* 5-Carboxy-5-methyl-Δ^1-pyrroline 1-oxide (0·80 g.) and potassium cyanide (0·37 g.) were dissolved in water (10 ml.) and left at room temperature for 6 hr. The solution was then passed through a column of Dowex 50 resin (H^+ form), and the acidic eluate evaporated. The *acid* product (0·75 g.) formed needles, m. p. 133—134° (decomp.), from ethyl acetate (Found: C, 49·3; H, 5·8; N, 16·4%; equiv., 175. $C_7H_{10}O_3N_2$ requires C, 49·4; H, 5·9; N, 16·5%; equiv., 170). Titration in aqueous solution gave an apparent pK_a 3·6. The infrared spectrum (mull) showed max. at 3250, 2245, and 1698 cm.$^{-1}$.

(d) 2 : 4 : 4*-Trimethyl*-Δ^1*-pyrroline* 1*-oxide.* This was recovered in 52% yield after attempted addition of hydrogen cyanide under the conditions of experiment (a); no cyano-derivative was obtained.

Alkaline Hydrolysis of 2*-Cyano*-Δ^1*-pyrroline* 1*-Oxides.*—(a) 2*-Cyano*-4 : 5 : 5*-trimethyl*-Δ^1*-pyrroline* 1*-oxide.* The nitrone-cyanide (4·1 g.) in 10% aqueous sodium hydroxide (40 ml.) was heated under reflux for 3 hr. and the solution then neutralised and extracted with chloroform. Evaporation of the extract gave 1*-hydroxy*-4 : 5 : 5*-trimethylpyrrolid*-2*-one* (1·1 g.), needles, m. p. 101—102° (from ether–light petroleum) (Found: C, 59·0; H, 9·2; N, 9·5. $C_7H_{13}O_2N$ requires C, 58·7; H, 9·2; N, 9·8%), $\nu_{max.}$ (mull) 3310, 3120, and 1680 cm.$^{-1}$. Titration in aqueous solution gave apparent pK_a 8·85. With ethanolic ferric chloric a deep reddish-purple colour developed.

The original aqueous solution was adjusted to pH 1 and again extracted with chloroform. The extract yielded 2*-carboxy*-4 : 5 : 5*-trimethyl*-Δ^1*-pyrroline* 1*-oxide* (2·4 g.), needles, m. p. 40—41° (from benzene) (Found: C, 55·9; H, 7·9; N, 8·3%; equiv., 172. $C_8H_{13}O_3N$ requires C, 56·1; H, 7·6; N, 8·2%; equiv., 171), $\lambda_{max.}$ (in 95% ethanol) 266 mμ (ε 8200). Titration in aqueous solution gave an apparent pK_a 2·85.

(b) 2*-Cyano*-5 : 5*-dimethyl*-Δ^1*-pyrroline* 1*-oxide.* The nitrone-cyanide (5·0 g.) was hydrolysed as in the previous experiment. Acidification to pH 1 and extraction with chloroform gave 2*-carboxy*-5 : 5*-dimethyl*-Δ^1*-pyrroline* 1*-oxide* (3·1 g.), needles, m. p. 86° (from ether–light petroleum) (Found: C, 53·6; H, 7·3; N, 8·9%; equiv., 160. $C_7H_{11}O_3N$ requires C, 53·5; H, 7·0; N, 8·9%; equiv., 157), apparent pK_a 2·80 in water, $\lambda_{max.}$ (in 95% ethanol) 265 mμ (ε 8600).

The mother-liquors from the crystallisation were evaporated, and an aqueous solution of the residue passed down a column of Dowex 1 × 2 (acetate form). Evaporation of the eluate gave 1*-hydroxy*-5 : 5*-dimethylpyrrolid*-2*-one* (1·0 g.), needles, m. p. 82—83° (from hexane) (Found: C, 55·9; H, 8·6; N, 10·7. $C_6H_{11}O_2N$ requires C, 55·8; H, 8·5; N, 10·9%), apparent pK_a 8·7 in water, $\nu_{max.}$ (mull) 3320, 3090, and 1678 cm.$^{-1}$.

An authentic sample of this hydroxamic acid was prepared by reduction of methyl 4-methyl-4-nitropentanoate (21 g.) with zinc dust (30 g.) and ammonium chloride (6 g.) in 50% aqueous

ethanol (150 ml.). The mixture was stirred for 4 hr., zinc and zinc oxide were removed and washed with hot 50% aqueous ethanol (3 × 50 ml.), and the filtrate and washings combined and evaporated below 60° to a syrup. This syrup was dissolved in 2N-hydrochloric acid (50 ml.) and extracted with chloroform; evaporation of the chloroform yielded the 1-hydroxy-pyrrolidone (4·8 g., 30%), m. p. 83° undepressed on admixture with a specimen from the previous experiment.

Thermal Decarboxylation of 2-Carboxy-Δ¹-pyrroline 1-Oxides.—(a) *2-Carboxy-4 : 5 : 5-trimethyl-Δ¹-pyrroline 1-oxide.* The acid (100 mg.) was heated at 140—150° for 3 min.; carbon dioxide was evolved. The oily residue was converted into the picrate (120 mg., 58%), yellow needles, m. p. 114° (from ethanol) undepressed on admixture with the picrate of 4 : 5 : 5-trimethyl-Δ¹-pyrroline 1-oxide. The infrared spectra of the picrates were identical over the range 4000—650 cm.$^{-1}$.

(b) *2-Carboxy-5 : 5-dimethyl-Δ¹-pyrroline 1-oxide.* Treated as described under (a) this acid (100 mg.) gave 5 : 5-dimethyl-Δ¹-pyrroline 1-oxide, isolated as the picrate (140 mg., 65%), m. p. and mixed m. p. 78—79°.

Addition of Grignard Reagents to Δ¹-Pyrroline 1-Oxides.—*2-Ethyl-5 : 5-dimethyl-Δ¹-pyrroline 1-oxide.* 5 : 5-Dimethyl-Δ¹-pyrroline 1-oxide (10·0 g., dried by distillation with benzene) in anhydrous ether (30 ml.) was added to ethereal ethylmagnesium bromide [from ethyl bromide (15 g.) and magnesium (3·4 g.)], and the mixture heated under reflux for 30 min. Excess of aqueous ammonium chloride was added, and the ether layer separated, dried (Na_2SO_4), and fractionated, to give *5-ethyl-1-hydroxy-2 : 2-dimethylpyrrolidine* (11·2 g., 89%), b. p. 50—53°/0·7 mm. (Found: C, 66·8; H, 12·1; N, 9·9. $C_8H_{17}ON$ requires C, 67·1; H, 12·0; N, 9·8%). Aerial oxidation of this product in aqueous ethanol containing copper acetate and ammonia gave the corresponding *nitrone* (10·0 g., 90%), b. p. 54—56°/0·2 mm., $\nu_{max.}$ (liquid film) 1600 cm.$^{-1}$. The *picrate* formed yellow needles, m. p. 71—72°, from ethanol (Found: C, 45·6; H, 5·0; N, 15·3. $C_{14}H_{18}O_8N_4$ requires C, 45·4; H, 4·9; N, 15·1%).

2 : 5 : 5-Trimethyl-Δ¹-pyrroline 1-oxide. This was prepared from 5 : 5-dimethyl-Δ¹-pyrroline 1-oxide (2·0 g.) by the action of methylmagnesium iodide in ether followed by copper-catalysed aerial oxidation of the intermediary hydroxylamine. The *nitrone picrate* (1·9 g.) formed yellow needles, m. p. 98°, from ethanol (Found: C, 43·8 H, 4·3; N, 15·4. $C_{13}H_{16}O_8N_4$ requires C, 43·8; H, 4·5; N, 15·7%).

3 : 3 : 5 : 5-Tetramethyl-Δ¹-pyrroline 1-oxide. 2 : 4 : 4-Trimethyl-Δ¹-pyrroline 1-oxide (10·0 g.) was treated with ethereal methylmagnesium iodide [from methyl iodide (22·4 g.) and magnesium (3·8 g.)], to give *1-hydroxy-2 : 2 : 4 : 4-tetramethylpyrrolidine* (9·0 g., 81%) which sublimed at 75°/14 mm. to colourless needles, m. p. 62° (Found: C, 66·7; H, 11·9; N, 9·9. $C_8H_{17}ON$ requires C, 67·1; H, 12·0; N, 9·8%). Copper-catalysed aerial oxidation of the hydroxylamine (8·5 g.) gave the *Δ¹-pyrroline 1-oxide* (6·0 g., 72%), b. p. 73°/1 mm., needles, m. p. 32—34° (from light petroleum) (Found: C, 67·7; H, 10·3; N, 9·6. $C_8H_{15}ON$ requires C, 68·0; H, 10·7; N, 9·9%). The *picrate* formed yellow needles, m. p. 137—138°, from ethanol (Found: C, 45·5; H, 4·9; N, 15·4. $C_{14}H_{16}O_8N_4$ requires C, 45·5; H, 4·9; N, 15·1%).

Addition of Nitro-alkanes to 5 : 5-Dimethyl-Δ¹-pyrroline 1-Oxide.—(*a*) Nitromethane (11·7 g.) in ethanol (50 ml.) was added to a stirred solution of the Δ¹-pyrroline 1-oxide (10·5 g.) and sodium ethoxide (from 1·8 g. of sodium) in ethanol (200 ml.) and left at room temperature overnight. After acidification with acetic acid (5 ml.) the ethanol was evaporated and the residue extracted with chloroform. Fractionation of the washed and dried (Na_2SO_4) extract gave *1-hydroxy-2 : 2-dimethyl-5-nitromethylpyrrolidine* (11·8 g., 74%) as a viscous yellow oil, b. p. 98°/0·3 mm. (Found: C, 48·5; H, 8·0; N, 16·3. $C_7H_{14}O_3N_2$ requires C, 48·3; H, 8·1; N, 16·1%), $\nu_{max.}$ (liquid film) 3220 and 1552 cm.$^{-1}$.

(*b*) In a similar fashion nitroethane (12·6 g.) was added to the Δ¹-pyrroline-1-oxide (9·5 g.), to give *1-hydroxy-2 : 2-dimethyl-5-1′-nitroethylpyrrolidine* (3·7 g.), b. p. 100—102°/0·4 mm. (Found: C, 50·8; H, 8·8; N, 15·0. $C_8H_{16}O_3N_2$ requires C, 51·1; H, 8·6; N, 14·9%), $\nu_{max.}$ (liquid film) 3480 and 1548 cm.$^{-1}$. Part of the Δ¹-pyrroline 1-oxide (5·7 g.) was recovered.

Base-catalysed Condensation of 2 : 4 : 4-Trimethyl-Δ¹-pyrroline 1-Oxide with Aromatic Aldehydes.—(*a*) The Δ¹-pyrroline 1-oxide (0·50 g.), benzaldehyde (0·45 g.), and potassium hydroxide (50 mg.) in ethanol (4 ml.) were heated under reflux for 30 min., then poured into water, giving *4 : 4-dimethyl-2-styryl-Δ¹-pyrroline 1-oxide* (0·31 g.) as colourless needles, m. p. 113° (from benzene–light petroleum) (Found: C, 78·4; H, 8·3; N, 6·4. $C_{14}H_{17}ON$ requires C, 78·1; H, 8·0; N, 6·5%), $\nu_{max.}$ (mull) 1537, 990, 977, 756, and 691 cm.$^{-1}$, $\lambda_{max.}$ (in 95% ethanol) 236 and 329 mμ (ε 11,200 and 22,600).

(*b*) A similar condensation with *p*-nitrobenzaldehyde gave 4 : 4-*dimethyl*-2-4'-*nitrostyryl*-Δ^1-*pyrroline* 1-*oxide* as bright yellow leaflets, m. p. 233° (from ethanol) (Found: C, 64·4; H, 6·0; N, 10·9. $C_{14}H_{16}O_3N_2$ requires C, 64·6; H, 6·2; N, 10·8%).

Benzoylation of 2 : 4 : 4-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide*.—The pyrroline oxide (0·40 g.) was benzoylated with excess of benzoyl chloride and sodium hydroxide solution to give a semisolid product which was extracted with benzene. The dried (Na_2SO_4) extract was passed through a short column of alumina and concentrated: addition of light petroleum gave 5-*benzamido*-1-*benzoyloxy*-4 : 4-*dimethylpentan*-2-*one* (0·51 g.) as prisms, m. p. 117° (from 80% aqueous methanol) (Found: C, 71·2; H, 6·1; N, 4·0. $C_{21}H_{23}O_4N$ requires C, 71·4; H, 6·6; N, 4·0%), $\nu_{max.}$ (mull) 3360, 1718, 1637, and 1547 cm.$^{-1}$, $\lambda_{max.}$ (in 95% ethanol) 231 and 270 mμ (inflexion) (ε 25,700 and 1800). The product was insoluble in cold dilute acids and gave no colour with ferric chloride. Hydrolysis of this compound (113 mg.) with aqueous ethanolic potassium hydroxide gave benzoic acid (67 mg., 87%), identified by m. p. and mixed m. p. 119°. The 2 : 4-*dinitrophenylhydrazone* formed yellow prisms, m. p. 172° (from ethanol) (Found: C, 60·7; H, 4·9. $C_{27}H_{27}O_7N_5$ requires C, 60·8; H, 5·1%), $\lambda_{max.}$ (in 95% ethanol) 356—358 mμ (ε 21,900).

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, January* 20*th*, 1959.]

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424. *Experiments towards the Synthesis of Corrins. Part III.* Formation of a Bicyclic Oxaziran from a* Δ^1*-Pyrroline and from the Corresponding Nitrone.*

By R. BONNETT, V. M. CLARK, and SIR ALEXANDER TODD.

Irradiation of 5 : 5-dimethyl-Δ^1-pyrroline 1-oxide yields the bicyclic oxaziran (IV), also obtained by oxidation of 5 : 5-dimethylpyrroline with aqueous hydrogen peroxide. Thermal rearrangement of the oxaziran (IV) leads to 5 : 5-dimethylpyrrolid-2-one, whereas acidic hydrolysis yields lævulic aldehyde.

Investigation of a reported 3-hydroxyoxaziran shows it to be the isomeric hydroxamic acid.

RECENT investigations[1,2] have revived interest in compounds containing the three-membered carbon–nitrogen–oxygen (oxaziran) ring (I), a formulation at one time suggested for the nitrones (azomethine *N*-oxides) (II) only to be subsequently discarded. The oxazirans and the azomethine *N*-oxides might be regarded as *electronic* tautomers and, indeed, irradiation of nitrones can yield oxazirans,[3] thermal decomposition of which regenerates the original nitrones.[4]

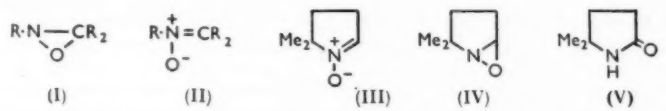
In the course of our work on Δ^1-pyrroline 1-oxides we irradiated 5 : 5-dimethyl-Δ^1-pyrroline 1-oxide[5] (III), whereupon the nitrone was converted into an isomer to which we assign the oxaziran structure (IV). The same material was obtained on oxidation of 5 : 5-dimethyl-Δ^1-pyrroline[6] with aqueous hydrogen peroxide.

The product is assigned structure (IV) on the basis of its analysis and active-oxygen content (cf. ref. 1), and the absence of ultraviolet absorption (in ethanol), of infrared maxima (liquid film) in the N–H and double-bond regions, and of basic properties. The

* Part II, preceding paper.

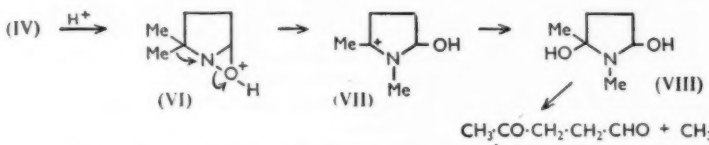
[1] Emmons, *J. Amer. Chem. Soc.*, 1956, **78**, 6208; 1957, **79**, 5739.
[2] Farbenfabriken Bayer, B.P. 743,940; Krimm, *Chem. Ber.*, 1958, **91**, 1057.
[3] Kamlet and Kaplan, *J. Org. Chem.*, 1957, **22**, 576; Splitter and Calvin, *ibid.*, 1958, **23**, 651.
[4] Hawthorne and Strahm, *ibid.*, 1957, **22**, 1263.
[5] Bonnett, Brown, Clark, Sutherland, and Todd, preceding paper.
[6] Bonnett, Clark, Giddey, and Todd, *J.*, 1959, 2087.

nuclear magnetic resonance spectrum of the liquid measured at 40 Mc./sec. exhibited chemical shifts σ of +1·0, +3·2, +3·9, +4·12, +4·34 (in parts per million relative to water) in accordance with the proposed structure.



(I) (II) (III) (IV) (V)

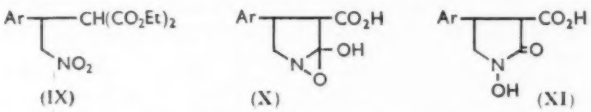
The compound (IV) behaved in a fashion analogous to the similarly substituted monocyclic oxazirans.[1] When it was heated, the nitrone (III) was not re-formed but, instead, there was a slow isomerisation to the corresponding amide, 5 : 5-dimethylpyrrolid-2-one



(V). Treatment with acid resulted in rearrangement to lævulaldehyde, isolable as its bisdinitrophenylhydrazone, the reaction possibly following the course (VI ⟶ VIII). No methylamine was detected, but the acidic solution gave a strong Ehrlich reaction as would be expected from pyrrole derivatives which might be formed from (VIII) or its equivalent.

Irradiation of 2-substituted Δ^1-pyrroline 1-oxides failed to yield oxazirans, as did oxidation of the corresponding pyrrolines, owing presumably to a combination of steric and electronic factors.

Reichert and Wegner[7] have reported that controlled catalytic reduction of the nitro-ester (IX; Ar = *o*-methoxyphenyl) followed by hydrolysis gave a compound $C_{12}H_{13}O_5N,H_2O$ for which they proposed structure (X). On the basis of present knowledge it is to be



(IX) (X) (XI)

expected that the product will be the related α-hydroxy-nitrone, existing as the tautomeric hydroxamic acid (XI). Repetition of Reichert and Wegner's work gave a product which, in accordance with structure (XI), exhibited carbonyl bands in the infrared spectrum at 1738 and 1667 cm.$^{-1}$ and on electrometric titration in aqueous solution had pK_a values of 2·5 and 7·2, corresponding to the carboxylic and hydroxamic acid respectively. It also gave a purple colour with ferric chloride.

Experimental

2 : 2-*Dimethyl*-6-*oxa*-1-*aza*bicyclo[3 : 1 : 0]*hexane*.—(a) *By oxidation of* 5 : 5-*dimethyl*-Δ^1-*pyrroline*. Hydrogen peroxide (20 ml. of " 30 vol.") was added to the pyrroline (11 g.) in water (15 ml.) and kept at 0° for 2 days, during which two layers were formed. A trace of platinum powder was added and after effervescence had subsided the suspension was extracted with ether (2 × 50 ml.): the extract was dried (Na_2SO_4) and evaporated, leaving the neutral liquid 2 : 2-*dimethyl*-6-*oxa*-1-*aza*bicyclo[3 : 1 : 0]*hexane* (8·2 g., 64%), b. p. 60°/32 mm. (Found: C, 63·9; H, 10·1; N, 11·8; active O, 13·6. $C_6H_{11}ON$ requires C, 63·7; H, 9·8; N, 12·4; active O, 14·2%). Under atmospheric pressure the b. p. was *ca.* 150° but on occasion explosion occurred at this temperature. The proton magnetic resonance spectrum of the liquid

[7] Reichert and Wegner, *Ber.*, 1938, **71**, 1254.

(*cyclo*hexane as internal standard) exhibited peaks with chemical shifts σ, −1·90 (very weak, possibly from impurity), +1·0 (H at $C_{(5)}$), +3·2, +3·9 (ring CH_2), +4·12, +4·34 (*gem*-dimethyl). The active-oxygen titre of an aqueous solution of the oxaziran decreased to half its initial value in 30 days.

(b) *By irradiation of* 5 : 5-*dimethyl*-Δ^1-*pyrroline* 1-*oxide*. The nitrone [5] (1·6 g.) in *cyclo*hexane–ethanol (10 ml. of each) was placed 10 mm. from an Hanovia UVS 250 lamp and irradiated for 5 days. Fractionation of the product gave the crude oxaziran (0·18 g., 11%; b. p. 55—60°/25 mm.) whose infrared spectrum (liquid film) contained the same strong peaks in the fingerprint region as that of the oxidation product of the pyrroline; the active-oxygen titre was 12·6%. The infrared spectrum (film) of the distillation residue showed maxima corresponding to unchanged nitrone and the pyrrolidone (V) derived by thermal rearrangement of the oxaziran.

Action of Heat upon the Oxaziran (IV).—Infrared spectroscopy indicated little change in a solution of the oxaziran (0·4 g.) in *cyclo*hexane (1 ml.) kept under reflux for 36 hr. Removal of the solvent and elevation of the temperature to 130° for 14 hr. brought about development of a strong band at 1690 $cm.^{-1}$. After removal of unchanged oxaziran under reduced pressure, sublimation of the residue yielded a small quantity of a deliquescent solid, m. p. 36—38° (lit.,[8] 37—41°) whose infrared spectrum was consistent with the product's being 5 : 5-dimethylpyrrolid-2-one.

Action of Acid upon the Oxaziran (IV).—Dissolution of the oxaziran (0·66 g.) in 50% sulphuric acid (2 ml.) was accompanied by a rise in temperature and the development of a red colour; an Ehrlich test on this solution was strongly positive. The solution was heated for 10 min. on a steam-bath, diluted with 1 : 1 aqueous ethanol (20 ml.), and treated with 2 : 4-dinitrophenylhydrazine in methanolic hydrogen chloride, whereupon the bis-2 : 4-dinitrophenylhydrazone of lævulic aldehyde separated (0·33 g., 13%), having m. p. 237°: undepressed on admixture with a sample prepared from sylvan [9] (Found: C, 44·3; H, 3·75; N, 24·1. Calc. for $C_{17}H_{16}O_8N_8$: C, 44·3; H, 3·5; N, 24·2%). The infrared spectra of the two samples were identical.

Repetition of Reichert and Wegner's Experiment.—The nitro-diester (3 g.) obtained by addition of malonic ester to the condensation product of nitromethane and *o*-methoxybenzaldehyde [7] was hydrogenated in methanol at room temperature over platinum oxide. After 2 mols. of hydrogen had been absorbed the catalyst and solvent were removed, the residue was dissolved in ether, and the product extracted with aqueous alkali. Acidification gave a crystalline precipitate (0·55 g., 23%), recrystallisation of which from water gave 1-*hydroxy*-4-*o*-*methoxyphenyl*-2-*oxopyrrolidine*-3-*carboxylic acid monohydrate*, m. p. 130° (Found: C, 53·6; H, 5·8; N, 5·25. $C_{12}H_{13}O_5N,H_2O$ requires C, 53·5; H, 5·6; N, 5·2%). The infrared spectrum showed principal maxima at 3435, 3140, 2550, 1738, and 1667 $cm.^{-1}$; electrometric titration in water gave pK_{a_1} 2·5, pK_{a_2} 7·2, equiv. 132 (required, 135). The product gave a purple colour with ferric chloride solution, as did the residue arising from thermal decarboxylation at 160°.

This work was carried out during the tenure of a Salters' Fellowship (to R. B.).

University Chemical Laboratory, Cambridge. [*Received, January 20th*, 1959.]

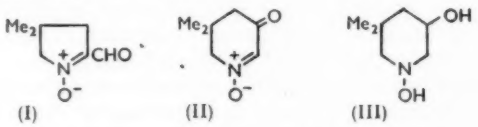
[8] Moffett and White, *J. Org. Chem.*, 1952, **17**, 407.
[9] Wilson, *J. Amer. Chem. Soc.*, 1948, **70**, 1313.

425. *Experiments towards the Synthesis of Corrins. Part IV.* The Oxidation and Ring Expansion of 2 : 4 : 4-Trimethyl-Δ¹-pyrroline 1-Oxide.*

By R. F. C. Brown, V. M. Clark, and Sir Alexander Todd.

2 : 4 : 4-Trimethyl-Δ¹-pyrroline 1-oxide, on oxidation with selenium dioxide and treatment of the product with acid, undergoes ring expansion to 1 : 2 : 3 : 4-tetrahydro-3 : 3-dimethyl-5-oxopyridine 1-oxide (II); the latter, on Clemmensen reduction, gives 2 : 4 : 4-trimethyl-Δ¹-pyrroline by ring contraction.

The nitrone group bears a marked resemblance to the carbonyl group both with respect to nucleophilic attack and in facilitating the removal of a proton under basic conditions from an α-carbon atom. Another well-recognised aspect of carbonyl chemistry is the oxidation of an adjacent methylene group to a carbonyl group by means of selenium dioxide;[1] with this reagent, too, the behaviour of Δ¹-pyrroline 1-oxides is clearly analogous. Thus, oxidation of 2 : 4 : 4-trimethyl-Δ¹-pyrroline 1-oxide[2] with selenium dioxide in methanol gave a dark oil whose reactions with carbonyl reagents were in accord with formula (I). However, when heated with N-hydrochloric acid, the dark oil was converted into a crystalline isomer which also gave derivatives with carbonyl reagents and to which we now assign structure (II).



(I) (II) (III)

The infrared spectrum of compound (II) showed strong bands at 1653 and 1546 cm.$^{-1}$ which could be attributed to a carbonyl and a nitrone group in conjugation, and a further strong band at 3030 cm.$^{-1}$ associated with the C–H stretching mode at unsaturated carbon. In the case of aldehydes this band is generally observed[3] at 2900—2700 cm.$^{-1}$, whereas Δ¹-pyrroline 1-oxides with a hydrogen atom at position 2 show the corresponding band near 3050 cm.$^{-1}$.[2] This spectral evidence suggested that, on treatment with acid, the aldehyde (I) had undergone ring opening with re-closure to form the ketone (II). The nuclear magnetic resonance spectrum, measured at 40 Mc./sec. for a carbon tetrachloride solution, supported this interpretation for, whereas the aldehydic hydrogen in a number of aldehydes examined in this laboratory has exhibited a chemical shift, σ, of $-4{\cdot}8 \pm 0{\cdot}7$ (in parts per million relative to water), the compound (II) gave a peak at σ −1·6; reference to 3 : 3 : 5 : 5-tetramethyl-Δ¹-pyrroline 1-oxide[2] disclosed a similar peak at σ −1·05 due undoubtedly to the CH of the nitrone grouping.

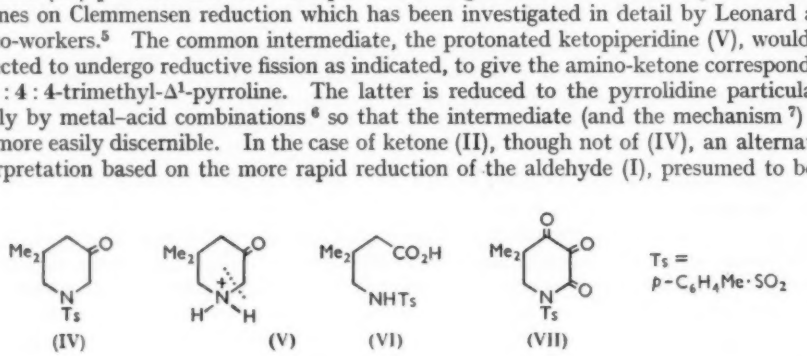
Whilst both the infrared and the nuclear magnetic resonance spectra supported structure (II), Clemmensen reduction of the compound gave 2 : 4 : 4-trimethyl-Δ¹-pyrroline, the product expected of (I). Reduction of compound (II) by aqueous potassium borohydride gave the crystalline β-hydroxy-hydroxylamine (III), but attempts to reduce this further to 3 : 3-dimethylpiperidine were unsuccessful. With phosphorus and hydriodic acid at 160°, the product (III) gave 5-hydroxy-3 : 3-dimethylpiperidine, and at 210° the product was an unidentified aliphatic amine, $C_7H_{17}N$. 5-Hydroxy-3 : 3-dimethylpiperidine with toluene-*p*-sulphonyl chloride and aqueous sodium hydrogen carbonate gave an oil

* Part III, preceding paper.

[1] Rabjohn in "Organic Reactions," ed. Adams, Wiley, New York, 1949, Vol. V, p. 331.
[2] Bonnett, Brown, Clark, Sutherland, and Todd, *J.*, 1959, 2094.
[3] Bellamy, "The Infra-Red Spectra of Complex Molecules," Methuen, London, 2nd edn., 1958, p. 156.

XUM

which contained a substantial amount of the *N*-toluene-*p*-sulphonyl derivative, for on oxidation with chromic acid in acetone [4] it afforded the crystalline ketone (IV). Clemmensen reduction of this ketone removed the toluene-*p*-sulphonyl group but the product was again 2 : 4 : 4-trimethyl-Δ^1-pyrroline. The formation of this base from both ketones (II) and (IV) provides another example of the ring contraction of homocyclic α-amino-ketones on Clemmensen reduction which has been investigated in detail by Leonard and his co-workers.[5] The common intermediate, the protonated ketopiperidine (V), would be expected to undergo reductive fission as indicated, to give the amino-ketone corresponding to 2 : 4 : 4-trimethyl-Δ^1-pyrroline. The latter is reduced to the pyrrolidine particularly slowly by metal–acid combinations [6] so that the intermediate (and the mechanism [7]) are the more easily discernible. In the case of ketone (II), though not of (IV), an alternative interpretation based on the more rapid reduction of the aldehyde (I), presumed to be in



(IV) (V) (VI) (VII)

equilibrium with ketone (II) in the strongly acidic medium, is possible but less likely. Treatment of the ketone (IV) with *p*-nitrosodimethylaniline in alkaline solution, followed by acid hydrolysis, gave a mixture. The acidic fraction yielded ββ-dimethyl-γ-toluene-*p*-sulphonamidobutyric acid (VI) whose formation is consonant with the structure allotted to the ketone (IV) and, hence, with that of the original ketone (II).

Catalytic hydrogenation of the ketone (II) in ethanol over platinum gave 5-hydroxy-3 : 3-dimethylpiperidine, three mols. of hydrogen being absorbed. This ready hydrogenolysis of the N–O bond is unusual amongst cyclic nitrones; dimeric 1 : 2 : 3 : 4-tetrahydropyridine 1-oxide on hydrogenation over platinum in acidic ethanol gives only 1-hydroxypiperidine [8] and previously we have obtained only 1-hydroxypyrrolidines from hydrogenation of Δ^1-pyrroline 1-oxides. The hydrogenation was also unusual in that the solution developed a deep red colour which was discharged abruptly after two mols. of hydrogen had been absorbed: the rate of absorption of the third mol. was much slower.

Experimental

1 : 2 : 3 : 4-*Tetrahydro*-3 : 3-*dimethyl*-5-*oxopyridine* 1-*Oxide*.—2 : 4 : 4-Trimethyl-Δ^1-pyrroline 1-oxide [3] (4·5 g.) and selenium dioxide (3·93 g.) in methanol (30 ml.) were heated under reflux for 2 hr. Deposited selenium was filtered off, and the solution evaporated to leave a dark syrup. N-Hydrochloric acid (30 ml.) was added, the solution heated on the steam-bath for 30 min., and the newly precipitated selenium again removed. The new filtrate was continuously extracted with ether for 10 hr., and the extract dried (Na_2SO_4) and, after passage through a short column of alumina, evaporated to 15 ml.; addition of light petroleum (b. p. 40—60°) then induced crystallisation. Recrystallisation from ether–light petroleum gave 1 : 2 : 3 : 4-*tetrahydro*-3 : 3-*dimethyl*-5-*oxopyridine* 1-*oxide* (1·4 g., 28%) as pale yellow plates, m. p. 75° (Found: C, 59·6; H, 7·8; N, 9·9. $C_7H_{11}O_2N$ requires C, 59·6; H, 7·9; N, 9·9%), $\lambda_{max.}$ (in ethanol) 280 mμ (ε 17,500), $\nu_{max.}$ (mull) 3030, 1653, and 1546 cm.$^{-1}$. The 2 : 4-*dinitrophenylhydrazone* formed orange-red leaflets (from ethyl acetate–ethanol), m. p. 248° (decomp.) (Found: C, 48·5; H, 4·5; N, 21·8. $C_{13}H_{15}O_5N_5$ requires C, 48·6; H, 4·7; N, 21·8%), $\lambda_{max.}$ (in ethanol) 385 mμ (ε 33,400).

Clemmensen Reduction of **1 : 2 : 3 : 4-*Tetrahydro*-3 : 3-*dimethyl*-5-*oxopyridine* 1-*Oxide*.**—The

[4] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2548.
[5] Leonard and Wildman, *J. Amer. Chem. Soc.*, 1949, **71**, 3089, and succeeding papers.
[6] Bonnett, Clark, Giddey, and Todd, *J.*, 1959, 2087.
[7] Leonard and Sentz, *J. Amer. Chem. Soc.*, 1952, **74**, 1704.
[8] Thesing and Mayer, *Chem. Ber.*, 1956, **89**, 2159.

oxo-compound (200 mg.) and amalgamated zinc wool (4 g.) in 10N-hydrochloric acid (5 ml.) were heated together for 8 hr., further addition of hydrochloric acid (1 ml.) being made at hourly intervals. Subsequently the mixture was made alkaline and steam-distilled. Neutralisation of the first 40 ml. of distillate with ethanolic picric acid was accompanied by precipitation of a salt which, on recrystallisation from ethanol, afforded 2 : 4 : 4-trimethyl-Δ^1-pyrroline picrate (195 mg., 40%) as yellow needles, m. p. 193°, undepressed on admixture with an authentic sample.[6]

Reduction of 1 : 2 : 3 : 4-*Tetrahydro*-3 : 3-*dimethyl*-5-*oxopyridine* 1-*Oxide with Potassium Borohydride*.—The oxo-compound (0·50 g.) and potassium borohydride (0·50 g.) were dissolved in water (10 ml.) and kept at room temperature for 48 hr. Extraction with ether followed by evaporation of the solvent gave a colourless gum which crystallised from ether–light petroleum (b. p. 40—60°) to give 1 : 5-*dihydroxy*-3 : 3-*dimethylpiperidine* (0·47 g.) as prisms, m. p. 80° (Found: C, 58·2; H, 10·6; N, 9·7. $C_7H_{15}O_2N$ requires C, 57·9; H, 10·4; N, 9·7%). It readily reduced aqueous alkaline triphenyltetrazolium chloride.[9]

Reduction of 1 : 5-*Dihydroxy*-3 : 3-*dimethylpiperidine with Phosphorus and Hydriodic Acid*.—(*a*) The 1-hydroxypiperidine (250 mg.), red phosphorus (80 mg.), and 56% hydriodic acid (3 ml.) were heated in a sealed tube at 160° for 6 hr. The mixture was made alkaline and steam-distilled, and the distillate neutralised with hydrochloric acid. Evaporation yielded a crystalline residue which, on recrystallisation from ethanol–ether, gave 5-*hydroxy*-3 : 3-*dimethylpiperidine hydrochloride* as prisms, m. p. 200° (Found: C, 50·8; H, 9·9; N, 8·6. $C_7H_{16}ONCl$ requires C, 51·0; H, 9·7; N, 8·5%). The product did not reduce aqueous alkaline triphenyltetrazolium chloride. (*b*) The 1-hydroxypiperidine (150 mg.), red phosphorus (200 mg.), and 56% hydriodic acid (3 ml.) were heated at 210° for 14 hr. The product was isolated as the *picrate* which crystallised from methylene chloride–ether as pale yellow needles, m. p. 124° (Found: C, 45·5; H, 5·7; N, 16·2. $C_7H_{17}N,C_6H_3O_7N_3$ requires C, 45·3; H, 5·9; N, 16·3%).

Catalytic Hydrogenation of 1 : 2 : 3 : 4-*Tetrahydro*-3 : 3-*dimethyl*-5-*oxopyridine* 1-*Oxide*.—The oxo-compound (72 mg.) was hydrogenated over pre-reduced platinum oxide (10 mg.) in ethanol (10 ml.) at 25°, uptake of hydrogen (37 ml., 3 mol.) being complete in 20 min. Neutralisation of the filtered solution with hydrochloric acid, followed by evaporation and crystallisation of the residue from ethanol–ether, gave 5-hydroxy-3 : 3-dimethylpiperidine hydrochloride (73 mg.) as prisms, m. p. 200° undepressed on admixture with the product from the phosphorus–hydriodic acid reduction.

3 : 3-*Dimethyl*-5-*oxo*-1-*toluene*-p-*sulphonylpiperidine*.—1 : 2 : 3 : 4-Tetrahydro-3 : 3-dimethyl-5-oxopyridine 1-oxide (1 g.) in ethanol (30 ml.) was hydrogenated over platinum oxide (50 mg.), absorption being complete after 6 hr. The β-hydroxy-piperidine was isolated as the hydrochloride which, without purification, was shaken with saturated aqueous sodium hydrogen carbonate (20 ml.) and a solution of toluene-*p*-sulphonyl chloride (1·5 g.) in acetone (20 ml.). After 1 hr., 3N-sodium hydroxide (40 ml.) was added and the mixture warmed on the steam-bath to complete the hydrolysis of unchanged toluene-*p*-sulphonyl chloride. Extraction with ether followed by evaporation yielded a viscous yellow oil (1·9 g.) whose infrared spectrum showed it to be the required 5-hydroxy-1-toluene-*p*-sulphonyl compound. The crude oil was dissolved in acetone (30 ml.), and a solution (1·5 ml.; 8N with respect to oxygen [4]) of chromic acid in aqueous sulphuric acid added.

After 10 min., a few drops of propan-2-ol were introduced, the acetone evaporated, water added, and the product extracted with ether. The ethereal extract was filtered through a short column of alumina and concentrated (to 10 ml.). Addition of light petroleum (b. p. 40—60°) and recrystallisation of the precipitated product from ether–light petroleum gave 3 : 3-*dimethyl*-5-*oxo*-1-*toluene*-p-*sulphonylpiperidine* (0·7 g., 35%) as needles, m. p. 110° (Found: C, 59·7; H, 6·9; N, 5·2. $C_{14}H_{19}O_3NS$ requires C, 59·8; H, 6·8; N, 5·0%), $\nu_{max.}$ (mull) 1726 cm.$^{-1}$. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol as yellow needles, m. p. 190° (Found: C, 52·0; H, 4·8; N, 15·2. $C_{20}H_{23}O_6N_5S$ requires C, 52·1; H, 5·0; N, 15·2%).

Clemmensen Reduction of 3 : 3-*Dimethyl*-5-*oxo*-1-*toluene*-p-*sulphonylpiperidine*.—The ketone (200 mg.), acetic acid (1 ml.), 10N-hydrochloric acid (4 ml.), toluene (2 ml.), and amalgamated zinc wool (3 g.) were heated together under reflux for 5 hr. The solution was decanted from zinc amalgam and diluted to 25 ml. with water, and the non-basic material (which had a strong smell of thio-*p*-cresol) removed by extraction with ether. The aqueous solution was then made

[9] Snow, *J.*, 1954, 2588.

alkaline and steam-distilled. Neutralisation of the distillate with picric acid, evaporation to dryness, and recrystallisation of the residue from ethanol gave 2 : 4 : 4-trimethyl-Δ^1-pyrroline picrate as yellow needles (99 mg., 41%), m. p. and mixed m. p. 193°.

*Synthesis of ββ-Dimethyl-γ-toluene-*p*-sulphonamidobutyric Acid.*—ββ-Dimethylglutaric anhydride was converted by ammonolysis followed by Hofmann degradation in methanol into the crude urethane, ββ-dimethyl-γ-(methoxycarbonylamino)butyric acid, as described by Brown and van Gulick.[10]

The urethane (1·30 g.) was heated under reflux for 4 hr. with 5N-hydrochloric acid (4 ml.). Neutral material was then removed from the cooled solution by extraction with ether, and the aqueous solution evaporated to dryness. The crystalline residue was recrystallised from ethanol and ether to give *γ-amino-ββ-dimethylbutyric acid hydrochloride* (0·72 g.) as needles, m. p. 140° (Found: C, 43·2; H, 8·4; N, 8·5. $C_6H_{14}O_2NCl$ requires C, 43·0; H, 8·4; N, 8·4%).

To this hydrochloride (0·3 g.) and sodium hydrogen carbonate (0·5 g.) in water (20 ml.), toluene-*p*-sulphonyl chloride (0·8 g.) in acetone (20 ml.) was added. The mixture was shaken at room temperature for 3 hr., after which the acetone was evaporated, excess of toluene-*p*-sulphonyl chloride removed by extraction with ether, and the aqueous solution acidified to give the *toluene*-p-*sulphonamido-acid* (0·16 g.), which formed needles, m. p. 148° (Found: C, 54·5; H, 6·6; N, 5·0. $C_{13}H_{19}O_4NS$ requires C, 54·7; H, 6·7; N, 4·9%).

Reaction of 3 : 3-*Dimethyl-5-oxo-*1-*toluene-*p-*sulphonylpiperidine with* p-*Nitrosodimethylaniline.*—The ketone (220 mg.) and *p*-nitrosodimethylaniline (120 mg., 1 mol.) in ethanol (5 ml.) containing aqueous 3N-sodium hydroxide (2 drops) were left at room temperature for 15 hr., after which the ethanol was evaporated and 10N-hydrochloric acid (3 ml.) added. The acidic solution was heated on the steam-bath for 15 min., diluted to 20 ml. with water, and extracted with ether; the extract was separated into an acidic and a neutral fraction by extraction with aqueous sodium hydrogen carbonate. The acidic fraction was crystalline and after several recrystallisations from ether–light petroleum (b. p. 40—60°) gave ββ-dimethyl-γ-toluene-*p*-sulphonamidobutyric acid (23 mg.) as needles, m. p. and mixed m. p. 148° (Found: C, 55·0; H, 6·6. Calc. for $C_{13}H_{19}O_4NS$: C, 54·7; H, 6·7%). The infrared spectra of this and the previous specimen were identical.

The neutral fraction, a small quantity of yellow oil, failed to crystallise. On treatment with 2 : 4-dinitrophenylhydrazine in ethanolic sulphuric acid it gave a bright red precipitate which was recrystallised by adding ether to its solution in dimethylformamide containing a little acetic acid. This afforded small red prisms of a *bis*-2 : 4-*dinitrophenylhydrazone*, m. p. 256° (decomp.) (Found: C, 46·9; H, 4·2; N, 19·2. $C_{26}H_{23}O_{11}N_9S$ requires C, 46·6; H, 3·5; N, 18·8%). Its infrared spectrum showed a carbonyl band at 1665 cm.$^{-1}$ in addition to bands at 1610 and 1587 cm.$^{-1}$ (Nujol mull). In the visible and ultraviolet region, maxima occurred at 397 mμ (ε 37,900) and 439 mμ (ε 36,300) (in chloroform solution containing 5% of neutral dimethylformamide). As the bis-2 : 4-dinitrophenylhydrazone of 3 : 3-dimethyl*cyclo*hexane-1 : 2-dione [11] has $\lambda_{max.}$ 351 (ε 32,600) and 388 mμ (ε 25,700) it is probable that our product is a derivative of 3 : 3-dimethyl-4 : 5 : 6-trioxo-1-toluene-*p*-sulphonylpiperidine (VII). In aqueous-ethanolic sodium hydroxide it gave a deep blue solution.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, January 20th*, 1959.]

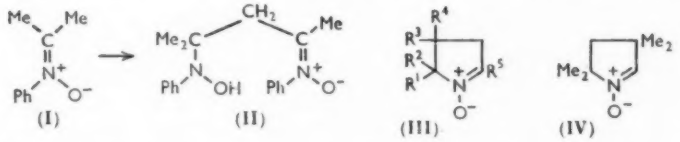
[10] Brown and van Gulick, *J. Amer. Chem. Soc.*, 1955, **77**, 1083.
[11] Ramirez and Bellet, *J. Amer. Chem. Soc.*, 1954, **76**, 491.

426. *Experiments towards the Synthesis of Corrins. Part V.* Base-catalysed Aldol-type Reactions of Δ^1-Pyrroline 1-Oxides.*

By R. F. C. Brown, V. M. Clark, I. O. Sutherland, and Sir Alexander Todd.

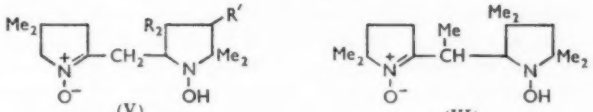
The base-catalysed formation of aldol-type products from cyclic nitrones of the Δ^1-pyrroline 1-oxide series is described; also conversion of the resulting nitrone-hydroxylamines into the bishydroxylamines and dipyrrolinylmethanes is discussed.

Banfield and Kenyon [1] in their work upon the reaction between acetone and phenylhydroxylamine showed that the nitrone (I) first formed dimerised spontaneously to the aldol-type product (II), and recently Thesing and Mayer [2] reported the condensation



(I) (II) (III) (IV)

product of butyraldehyde and phenylhydroxylamine [3] to be of the same type. The cyclic nitrones (III; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$; and $R^1 = R^2 = R^3 = Me$, $R^4 = R^5 = H$),[4] however, show little tendency to form aldolic dimers when stored at room temperature, though by basic catalysis aldol-type reactions can be brought about. Thus, the anion of the former nitrone generated by triphenylmethylsodium or sodamide in liquid ammonia has been added to the nitrones (III; $R^1 = R^2 = R^3 = Me$, $R^4 = R^5 = H$) and (IV) to yield the corresponding nitrone-hydroxylamines (Va and b)



(V) (VI)

a : R = H, R′ = Me
b : R = Me, R′ = H

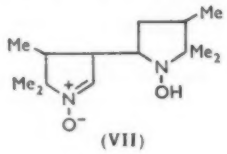
in the di-2-pyrrolidinylmethane series. The isolation of a single product (Vb) suggests that isomerism arising from a reversal of oxidation level in the two rings is absent; the formation of two isomeric products (Va) on use of triphenylmethylsodium can then be attributed to geometrical isomerism arising from the relative positions of the bridging methylene group and the isolated methyl group (R′). Use of sodamide in liquid ammonia gave only one isomer of (Va) and to this we assign the *trans*-configuration. Addition of the nitrone (III; $R^1 = R^2 = Me$, $R^3 = R^4 = H$, $R^5 = Et$) to (IV) in the presence of sodamide in liquid ammonia also gave a single product which we formulate as the nitrone-hydroxylamine (VI). As the monomeric nitrones (III; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$; and $R^1 = R^2 = R^3 = Me$, $R^4 = R^5 = H$) are isomeric it was of importance to determine whether the nitrone-hydroxylamines (Va) were derived from either compound alone or were the products of addition of one nitrone to the other. Attempted base-catalysed dimerisation of the first of this pair by triphenylmethylsodium failed whilst, under the same conditions, the second of the pair gave a dimer (VII).

The infrared spectrum of the *trans*-product (Va) showed bands at 3130 (OH group)

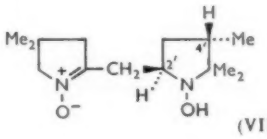
* Part IV, preceding paper.

[1] Banfield and Kenyon, *J.*, 1926, 1612.
[2] Thesing and Mayer, *Chem. Ber.*, 1956, **89**, 2159.
[3] Utzinger and Regenass, *Helv. Chim. Acta*, 1954, **37**, 1892.
[4] Bonnett, Brown, Clark, Sutherland, and Todd, *J.*, 1959, 2094.

and at 1614 cm.$^{-1}$ (2-substituted nitrone [4]). The presence of the hydroxylamine group was confirmed by the colour test with triphenyltetrazolium chloride,[5] and that of the nitrone group by its ultraviolet absorption at 233 mμ. Since the 2-methyl group of the nitrone (III; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$) had been shown to undergo condensation with aromatic aldehydes [4] whilst the 3-methylene group of the nitrone (III; $R^1 = R^2 = R^3 = Me$, $R^4 = R^5 = H$) did not, and since the former nitrone did not undergo dimerisation

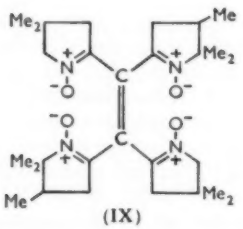


(VII)

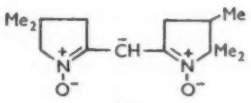


(VIII)

in the presence of triphenylmethylsodium, it can be concluded that addition to give products represented as (Va) had indeed taken place. The reactions of these compounds are entirely consistent with this structure. In the formation of (Va) in presence of triphenylmethylsodium the two isomers were obtained in 30% and 8% yield respectively; on oxidation they gave the same product and we suggest that these isomers are respectively the 2' : 4'-*trans*- and 2' : 4'-*cis*-compounds (VIII; *trans*-form shown). Aerial oxidation of either isomer in the presence of ammonia and a catalytic amount of cupric ion gave a bright yellow product, $C_{28}H_{44}O_4N_4$, evidently formed by oxidative dimerisation. The infrared spectrum of this product showed no absorption in the hydroxyl region and a single strong band in the nitrone region, at 1542 cm.$^{-1}$, which we assign to nitrone groups in conjugation with an unsaturated system. As there were no bands indicative of CH out-of-plane vibrations, it appeared that the new double bond (required by the analytical figures) was tetrasubstituted. The ultraviolet spectrum exhibited a sharp band at 256 mμ (ε 13,200) and a broad band at 380—390 mμ (ε 10,400); on this evidence we assign structure (IX) to the product and assume that it was formed by oxidative dimerisation of the anion (X) of the intermediate dinitrone, followed by a further oxidative step. In the pyrrole series analogous oxidations of dipyrrylmethanes to tetrapyrrylethanes and tetrapyrrylethylenes are well known.[6] Examination of a model of (IX) suggests that



(IX)



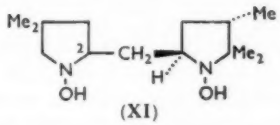
(X)

when two rings are coplanar and their nitrone groups fully conjugated, the other two rings cannot also be coplanar. In all probability the rings are inclined with respect to the plane of the central ethylenic bond and this would account for the low intensity of the long-wavelength band in the ultraviolet spectrum. A further stereochemical complication exists arising from the non-identity of the ring-substituents, *cis*- and *trans*-ethylenes being possible; that shown in (IX) is the *trans*-ethylene. The compound could not be obtained in well-formed crystals and, although it appeared to be homogeneous when subjected to paper chromatography, it may well have been a mixture of geometrical isomers.

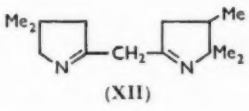
Reduction of the *trans*-compound (VIII) with aqueous potassium borohydride gave

[5] Rogers, *J.*, 1955, 769; Snow, *J.*, 1954, 2588.
[6] Fischer, Baumgartner, and Plötz, *Annalen*, 1932, **493**, 9; Fischer and Beller, *ibid.*, 1925, **444**, 239.

the corresponding bishydroxylamine (XI): in consequence of the additional asymmetric centre generated at $C_{(2)}$ two diastereoisomers were obtained, although one, m. p. 156°, was formed in much greater amount than the other, m. p. 134°. Reactions expected to yield the corresponding dipyrrolinylmethanes (XII) gave, in addition, other products, the



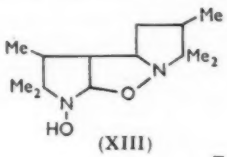
(XI)



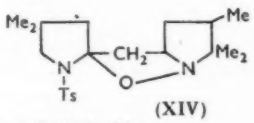
(XII)

nature of which became apparent from the detailed study of the aldonitrone dimer (VII).

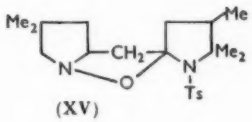
The infrared spectrum of the dimer (VII), measured in Nujol mulls, showed a strong band at 3240 cm.$^{-1}$ indicative of a hydroxyl group, but no nitrone absorption in the region 1620—1570 cm.$^{-1}$. The ultraviolet spectrum, measured in ethanol, exhibited a band at 236 mμ, indicating the presence of a nitrone group; the intensity (ε 6000), however, was lower than previously observed [4] for the simple cyclic nitrones (ε *ca.* 10,000). In *cyclo*hexane solution this ultraviolet band was shifted to 249 mμ, the intensity then being normal (ε 11,800). Again, the infrared spectrum of the dimer (VII) in chloroform solution showed both hydroxyl (3680, 3560 cm.$^{-1}$) and nitrone (1583 cm.$^{-1}$) absorption. The evidence suggests an equilibrium sensitive to changes of state and of solvents, and most likely to be attributable to reversible addition of the hydroxyl group of the hydroxylamino-group to the double bond of the nitrone group to give the tricyclic system (XIII).



(XIII)



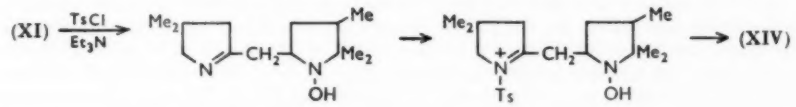
(XIV)



(XV)

Ts = *p*-$C_6H_4Me\cdot SO_2$

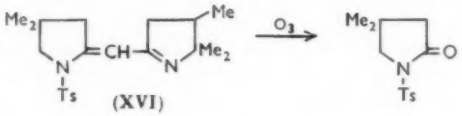
The bishydroxylamine (XI) on treatment with three mols. of toluene-*p*-sulphonyl chloride and excess of triethylamine (cf. ref. 4) gave a mixture separable into two main fractions by chromatography on neutral alumina: each fraction yielded a crystalline base. The first product, $C_{21}H_{32}O_3N_2S$, exhibited the ultraviolet maximum at 228 mμ (ε 9900) and an inflexion at 260—265 mμ (ε 1800) to be expected of a toluene-*p*-sulphonamide. The infrared spectrum showed neither hydroxyl absorption nor strong bands in the 1700—1500 cm.$^{-1}$ region. As the toluene-*p*-sulphonyl group accounts for two of the three oxygen atoms present and there is no carbonyl or hydroxyl group, the remaining oxygen atom must be located either in a toluene-*p*-sulphonyl ester or in an ether linkage. The molecular formula requires that the heterocyclic part of the molecule should be either tricyclic and saturated, or bicyclic with a single double bond. A double bond if present would almost certainly have been detected in the infrared or ultraviolet spectrum and the introduction of an isolated 3 : 4-double bond into a pyrrolidine ring under such mild conditions is in any case unlikely. The only structures which readily accommodate the evidence are the isomeric *spiro*-structures (XIV) and (XV) of which the former is preferred since its



formation would involve initial attack at the less hindered hydroxylamine group of (XI). The *spiro*-compound (XIV) could arise by ordinary *O*-esterification of (XI) followed by

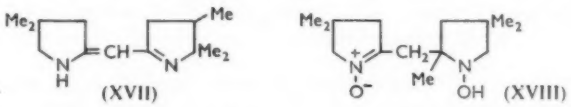
elimination of toluene-*p*-sulphonic acid to give the pyrroline-hydroxylamine and the acylation of this to give the *spiro*-structure.

The second product of interaction of (XI) with toluene-*p*-sulphonyl chloride had a molecular formula $C_{21}H_{30}O_3N_2S$, differing from (XIV) by the elements of water. Its infrared spectrum showed the toluene-*p*-sulphonyl group to be present (C:C ring stretching at 1600 and 1495 cm.$^{-1}$; sulphone absorption at 1343 and 1164 cm.$^{-1}$); there was no hydroxyl absorption, all the oxygen atoms being accounted for by the toluene-*p*-sulphonyl group. In addition, there were two very strong bands at 1637 and 1580 cm.$^{-1}$: as the formula requires two double bonds to be present these bands may be assigned to a C=N and C=C group in conjugation. The presence of a conjugated unsaturated system in the heterocyclic portion of the molecule was confirmed by the ultraviolet spectrum of the base, which, in addition to the short-wavelength maximum at 227 mμ (ε 12,900), attributable to the toluene-*p*-sulphonyl group, showed a band of high intensity (ε 12,400) at 278 mμ. To this base we assign structure (XVI), an assignment supported by its ozonolysis



(XVI)

to 4 : 4-dimethyl-1-toluene-*p*-sulphonylpyrrolid-2-one, which on hydrolysis gave ββ-dimethyl-γ-toluene-*p*-sulphonamidobutyric acid. Treatment of the bishydroxylamine (XI) with phosphorus oxychloride and triethylamine gave a 63% yield of a dipyrrolinylmethane derivative whose high basicity (pK_a 12·1) and spectral characteristics (cf. ref. 7) showed it to exist as the vinylogous amidine (XVII); it gave the amide (XVI) on toluene-*p*-sulphonylation. Being the nitrogen analogue of a β-diketone, the product (XVII) readily formed a cobaltous and a cupric complex, both of which were soluble in light petroleum.



From our experiments it is apparent that, under the influence of strongly basic catalysts, aldol-type products can be obtained from the Δ^1-pyrroline 1-oxides. On one occasion only did we observe spontaneous dimerisation, that of the oxide (III; $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = Me$) to a product whose properties accord with structure (XVIII): storage over alkaline catalysts seemed not to effect the dimerisation, nor did irradiation, although samples of the nitrone which had been kept for long periods reduced the triphenyltetrazolium chloride reagent,[5] a reaction characteristic of the dimer, and not of the monomer.

Experimental

Addition of 2 : 4 : 4-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide to* 4 : 5 : 5-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide*—(*a*) A mixture of the pyrroline oxides (3·0 g. of each) was dried by azeotropic distillation with benzene and treated with a solution of triphenylmethylsodium (from triphenylmethyl chloride, 7·0 g., and 1·2% sodium amalgam, 120 g.) in anhydrous ether (300 ml.) in a closed evacuated apparatus which also served for the preparation of the reagent. After two days the ethereal solution was extracted with dilute hydrochloric acid. The acid extract was made alkaline with ammonia, and extracted with chloroform (4 × 20 ml.). The chloroform extract was dried (K_2CO_3), filtered through a short column of alumina, and evaporated. Recrystallisation of the solid residue from benzene–light petroleum gave clusters of large colourless needles of 2′ : 4′-trans-2-(1′-*hydroxy*-4′ : 5′ : 5′-*trimethylpyrrolidin*-2′-*ylmethyl*)-4 : 4-*dimethyl*-Δ^1-*pyrroline*

[7] Lloyd and Marshall, *J.*, 1958, 118.

1-*oxide* (VIII) (1·80 g., 30%), m. p. 136°, $\lambda_{max.}$ (in 95% ethanol) 233 mμ (ε 11,100); $\nu_{max.}$ (mull) 3130 and 1614 cm.$^{-1}$ [Found: C, 66·2; H, 10·1; N, 10·9%; *M* (thermistor method [8]), 263. $C_{14}H_{26}O_2N_2$ requires C, 66·1; H, 10·3; N, 11·0%; *M*, 254]. It readily reduced aqueous alkaline triphenyltetrazolium chloride solution, and even in the solid state the crystals quickly became pale yellow through autoxidation to the yellow oxidation product described below.

The benzene–light petroleum mother-liquors from the crystallisation of the above product were evaporated and stirred with a little water; sticky crystals separated. The mixture was diluted with water (20 ml.) and extracted with ether (4 × 15 ml.). The ethereal extract was evaporated and the residue recrystallised from benzene–light petroleum, giving small colourless prisms of the isomeric 2′ : 4′-cis-*nitrone-hydroxylamine* (0·50 g., 8%), m. p. 171°, $\nu_{max.}$ 3190 and 1624 cm.$^{-1}$ (Found: C, 66·0; H, 10·2; N, 10·9%). It readily reduced aqueous alkaline triphenyltetrazolium chloride solution, but the crystalline substance remained colourless, even on long storage.

(*b*) (By Dr. H. Moncure, jun.) 2 : 4 : 4-Trimethyl-Δ^1-pyrroline 1-oxide (11·0 g.) which had been dried by azeotropic distillation with benzene was treated with a solution of sodamide [from sodium (3·5 g.) in liquid ammonia (500 ml.) in the presence of a trace of ferric nitrate]. After 1 hr. at room temperature, the solution was treated with 4 : 5 : 5-trimethyl-Δ^1-pyrroline 1-oxide (10·5 g., dried by azeotropic distillation with benzene). The mixture was stirred and the liquid ammonia allowed to evaporate until a slurry remained (2—3 hr.). Water (500 ml.) was added cautiously to the semi-solid residue, and the solution extracted with chloroform (5 × 100 ml.); the extract was dried (K_2CO_3) and evaporated. Recrystallisation of the crude solid from benzene–light petroleum gave colourless needles of the *trans*-nitrone-hydroxylamine (15·6 g., 74%), m. p. 136° alone or mixed with the compound prepared as in (*a*).

Extraction of the benzene–light petroleum mother-liquors as in (*a*) failed to yield any of the *cis*-isomer.

Copper-catalysed Oxidation of the Nitrone-hydroxylamines (Va).—(*a*) The above *trans*-nitrone-hydroxylamine, m. p. 136° (0·51 g.), and copper sulphate (0·01 g.) were dissolved in water (10 ml.) and ammonia (1 ml.; *d* 0·880), and air was bubbled through the solution for 2 hr. The solution was extracted with chloroform (5 × 10 ml.), and the chloroform extract evaporated to give a bright yellow gum. This was chromatographed in light petroleum on a column of magnesium carbonate (50 g.). The yellow band was eluted with benzene–light petroleum, and the eluate evaporated to give a yellow solid. Recrystallisation from light petroleum containing a little benzene gave yellow prisms (0·34 g., 68%) of 1 : 2-*di*-(4 : 4-*dimethyl*-Δ^1-*pyrrolin*-2-*yl*)-1 : 2-*di*-(4 : 5 : 5-*trimethyl*-Δ^1-*pyrrolin*-2-*yl*)*ethylene tetra*-N-*oxide* (IX), m. p. 201° (decomp.), $\lambda_{max.}$ (in 95% ethanol) 256 and 380—390 mμ (ε 13,200 and 10,400), $\nu_{max.}$ (mull) 1542 cm.$^{-1}$ [Found: C, 67·0; H, 9·0; N, 11·3%; *M* (micro-Rast), 447. $C_{28}H_{44}O_4N_4$ requires C, 67·2; H, 8·9; N, 11·2%; *M*, 501].

(*b*) The *cis*-nitrone-hydroxylamine (0·10 g.) was oxidised and the product isolated as in (*a*), to give the same yellow oxidation product (0·04 g.), identified by m. p. and mixed m. p. 201° (decomp.).

Reduction of Compound (VIII) *with Potassium Borohydride.*—The *trans*-nitrone-hydroxylamine, m. p. 136° (0·51 g.), and potassium borohydride (0·5 g.) were dissolved in water (10 ml.) and left at room temperature for 48 hr. A crystalline precipitate was then collected and, after drying, weighed 0·31 g. Extraction of the filtrate with ether yielded a colourless gum (0·11 g.). The crystals and the gum were combined and recrystallised from low-boiling light petroleum. Repeated recrystallisation, finally from ethanol, gave rosettes of small needles (0·20 g.) of 1 : 1′-*dihydroxy*-4 : 4 : 4′ : 5′ : 5′-*pentamethyl*-2 : 2′-*dipyrrolidinylmethane*, m. p. 156°, $\nu_{max.}$ 3220 cm.$^{-1}$ (Found: C, 65·6; H, 10·9; N, 11·1. $C_{14}H_{28}O_2N_2$ requires C, 65·6; H, 11·0; N, 10·9%).

The light petroleum mother-liquors from the crystallisation were concentrated, and a small quantity of crystals which separated was collected. The filtrate was evaporated, and the sticky residue recrystallised several times from aqueous methanol. The material thus obtained was sublimed *in vacuo* (bath-temperature 100°/0·5 mm.) and again recrystallised from aqueous methanol, to give a diastereoisomeric *bishydroxylamine* as small feathery needles, m. p. 134° (Found: C, 65·7; H, 11·2; N, 11·1%). The m. p. of this compound was depressed below 120° in admixture with the compound of m. p. 156°. The infrared spectra of the two isomers were similar, but showed distinct differences in the fingerprint region.

Addition of 2 : 4 : 4-*Trimethyl*-Δ^1-*pyrroline* 1-*Oxide to* 3 : 3 : 5 : 5-*Tetramethyl*-Δ^1-*pyrroline*

[8] Iyengar, *Rec. Trav. chim.*, 1954, **73**, 789.

1-Oxide.—These pyrroline oxides (2·0 g. of each) were condensed in liquid ammonia (100 ml.) containing sodamide (from 0·7 g. of sodium), and the product isolated as described above. *2-(1′-Hydroxy-3′ : 3′ : 5′ : 5′-tetramethylpyrrolidin-2′-ylmethyl)-4 : 4-dimethyl-Δ¹-pyrroline 1-oxide* (Vb) (1·60 g., 40%) was obtained as needles (from methylene chloride–light petroleum), m. p. 150° (Found: C, 67·2; H, 10·4; N, 10·5. $C_{15}H_{28}O_2N_2$ requires C, 67·2; H, 10·4; N, 10·4%). The infrared spectrum (mull) showed maxima at 3110, 1635, and 1617 cm.$^{-1}$.

Addition of 2-Ethyl-5 : 5-dimethyl-Δ¹-pyrroline 1-Oxide to 3 : 3 : 5 : 5-Tetramethyl-Δ¹-pyrroline 1-Oxide.—These pyrroline oxides (1·5 g. of each) were condensed in liquid ammonia (100 ml.) containing sodamide (from 0·5 g. of sodium). Next morning water (40 ml.) was added, and the aqueous solution was extracted with chloroform. Evaporation of the chloroform extract yielded an oily mixture of product and starting materials. The latter were removed by sublimation at 90°/15 mm., and the crystalline non-volatile residue was recrystallised from light petroleum to give *2-[1-(1′-hydroxy-3′ : 3′ : 5′ : 5′-tetramethylpyrrolidin-2′-yl)ethyl]-5 : 5-dimethyl-Δ¹-pyrroline 1-oxide* (VI) (0·48 g., 16%) as prisms, m. p. 121—122° (Found: C, 68·1; H, 10·8; N, 9·8. $C_{16}H_{30}O_2N_2$ requires C, 68·0; H, 10·7; N, 9·9%), $\nu_{max.}$ (mull) at 3260 and 1590 cm.$^{-1}$.

The *picrate* formed needles (from ethanol), m. p. 144° (Found: C, 51·8; H, 6·8; N, 13·7. $C_{22}H_{33}O_9N_5$ requires C, 51·7; H, 6·5; N, 13·7%).

Dimerisation of 4 : 5 : 5-Trimethyl-Δ¹-pyrroline 1-Oxide with Ethereal Triphenylmethylsodium.—Triphenylmethylsodium (from triphenylmethyl chloride, 3·5 g., and 1·2% sodium amalgam, 50 g.) in anhydrous ether (200 ml.) was added to the pyrroline oxide (2·0 g.) in benzene (5 ml.) in a closed evacuated apparatus. The mixture was left overnight and then extracted with 3N-hydrochloric acid. The acidic extract was made alkaline with ammonia and extracted with ether (4 × 30 ml.). Evaporation of the ethereal extract and crystallisation of the residue from low-boiling light petroleum gave *3-(1′-hydroxy-4′ : 5′ : 5′-trimethylpyrrolidin-2′-yl)-4 : 5 : 5-trimethyl-Δ¹-pyrroline 1-oxide* (VII) (0·27 g., 13%) as clusters of small colourless needles, m. p. 142° [Found: C, 66·1; H, 10·0; N, 11·1%; *M* (thermistor method [8]), 278. $C_{14}H_{26}O_2N_2$ requires C, 66·1; H, 10·3; N, 11·0%; *M*, 254], $\lambda_{max.}$ 236 (ε 6000) in 95% ethanol, 249 mμ (ε 11,800) in *cyclo*hexane, $\nu_{max.}$ 3240 (Nujol mull) and 3680, 3560, and 1583 cm.$^{-1}$ (in chloroform).

Spontaneous Dimerisation of 2 : 4 : 4-Trimethyl-Δ¹-pyrroline 1-Oxide.—A sample of the pyrroline oxide (*ca.* 25 g.) which had been stored in the refrigerator for five months deposited a mass of crystals. This was collected on sintered glass, washed with benzene–light petroleum, and recrystallised from the same solvents to give a product (0·76 g.), possibly *2-(1′-hydroxy-2′ : 4′ : 4′-trimethylpyrrolidin-2′-ylmethyl)-4 : 4-dimethyl-Δ¹-pyrroline 1-oxide* (XVIII), as small colourless needles, m. p. 115° (Found: C, 66·3; H, 10·2; N, 10·8; active H, 0·52. $C_{14}H_{26}O_2N_2$ requires C, 66·1; H, 10·3; N, 11·0; active H, 0·40%], $\lambda_{max.}$ (in ethanol) 234 mμ (ε 9500), $\nu_{max.}$ 3320 and 1610 cm.$^{-1}$.

Aerial oxidation of the product (0·1 g.) in water (5 ml.) containing ammonia (1 ml.; *d* 0·880) and copper sulphate (10 mg.) gave, after extraction with methylene chloride, a dinitrone as a colourless hygroscopic gum. The *picrate* formed bright yellow prisms (from ethanol), m. p. 120° (Found: C, 50·0; H, 5·7; N, 15·7. $C_{20}H_{27}O_9N_5$ requires C, 49·9; H, 5·7; N, 14·55%). The base was regenerated from the picrate by passage of a methylene chloride solution through a short column of alumina. On evaporation the dinitrone was again obtained as a resin which could not be crystallised. The infrared spectrum showed maxima 1600 and 1591 cm.$^{-1}$.

Action of Toluene-p-sulphonyl Chloride and Triethylamine on a Bishydroxylamine.—1 : 1′-Dihydroxy-4 : 4 : 4′ : 5′ : 5′-pentamethyl-2 : 2′-dipyrrolidinylmethane, m. p. 156° (0·26 g.), and toluene-*p*-sulphonyl chloride (0·57 g., 3 mol.) were dissolved in dry pyridine (2·5 ml.), and the solution set aside for 30 min. Dry triethylamine (2·5 ml.) was then added, and the solution heated under reflux for a further 30 min. The solution was evaporated to dryness under reduced pressure and the residue shaken with ether and dilute ammonia. Evaporation of the ethereal solution gave a red gum, which was chromatographed in benzene–light petroleum (1 : 1) on a column of neutral alumina (25 g.). Benzene–light petroleum eluted a pale yellow gum (0·1 g.) (fraction A) and further elution with pure benzene gave a yellow gum (0·06 g.) (fraction B).

Fraction A on treatment with a slight excess of ethanolic picric acid afforded a crystalline *picrate*, which recrystallised from ethanol in lemon-yellow needles, m. p. 157° (Found: C, 52·5; H, 6·0; N, 11·7. $C_{27}H_{35}O_{10}N_5S$ requires C, 52·2; H, 5·7; N, 11·3%).

This picrate was converted into the free base by passage of its benzene solution through a

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short column of alumina. Evaporation of the benzene eluate and crystallisation of the residue from low-boiling light petroleum gave colourles platelets of 7 : 8 : 8 : 4′ : 4′-*pentamethyl*-1′-*toluene*-p-*sulphonyl*-2-*oxa*-1-*aza*bicyclo[3 : 3 : 0]*octane*-3-spiro-2′-*pyrrolidine* (XIV), m. p. 86—87° (Found: C, 64·4; H, 8·1; N, 7·0. $C_{21}H_{33}O_3N_2S$ requires C, 64·2; H, 8·2; N, 7·1%), $\lambda_{max.}$ (in 95% ethanol) 228 mμ (ε 9900) with an inflexion at 260—265 mμ (ε 1800), $\nu_{max.}$ (mull) 1600, 1498, 1349, and 1157 cm.$^{-1}$.

Fraction B on treatment with ethanolic picric acid precipitated a very sparingly soluble *picrate*, which was recrystallised from ethanol to give yellow prisms, m. p. 232° (decomp.) (Found: C, 53·5; H, 5·5; N, 11·6. $C_{27}H_{33}O_9N_5S$ requires C, 53·7; H, 5·5; N, 11·6%).

This was also converted into the base by chromatography on alumina from benzene solution. The crude base was recrystallised from light petroleum to give large colourless prisms of 2-(4′ : 4′-*dimethyl*-1′-*toluene*-p-*sulphonylpyrrolidin*-2′-*ylidenemethyl*)-4 : 5 : 5-*trimethyl*-Δ^1-*pyrroline* (XVI), m. p. 142° (Found: C, 67·3; H, 7·9; N, 7·7. $C_{21}H_{29}O_2N_2S$ requires C, 67·3; H, 8·1; N, 7·5%), $\lambda_{max.}$ (in 95% ethanol) 227 (ε 12,900) and 278 mμ (ε 12,400), $\nu_{max.}$ (mull) 1637, 1600, 1580, 1495, 1343, and 1164 cm.$^{-1}$.

Action of Phosphoryl Chloride and Triethylamine on a Bishydroxylamine.—To a solution of 1 : 1′-dihydroxy-4 : 4 : 4′ : 5′ : 5′-pentamethyl-2 : 2′-dipyrrolidinylmethane, m. p. 156° (4·80 g.), in anhydrous benzene (100 ml.) a solution of phosphoryl chloride (6·0 g.) in benzene (10 ml.) was added with cooling. A solution of triethylamine (9 ml.) in benzene (10 ml.) was then added dropwise, and the mixture was left at room temperature for 4 hr. After acidification with 3N-hydrochloric acid the mixture was distilled to remove benzene, and the remaining aqueous solution was cooled and extracted with ether (2 × 25 ml.) to remove non-basic material. 10N-Hydrochloric acid (50 ml.) was added, and the solution heated under reflux for 4 hr. It was then cooled, made strongly alkaline with sodium hydroxide, and extracted with ether (4 × 40 ml.). Evaporation of the ethereal extract gave a yellow gum which, on sublimation at 100° (bath-temperature)/20 mm., yielded substantially pure 2-(4′ : 4′-*dimethylpyrrolidin*-2′-*ylidenemethyl*)-4 : 5 : 5-*trimethyl*-Δ^1-*pyrroline* (XVII) as a pale yellow crystalline mass (2·61 g., 63%). Resublimation for analysis gave colourless crystals, m. p. 42° [Found: C, 76·4; H, 11·0; N, 12·9; *M* (micro-Rast), 231. $C_{14}H_{24}N_2$ requires C, 76·3; H, 11·0; N, 12·7%; *M*, 220], $\lambda_{max.}$ (in ether) 300 mμ (ε 17,500), (in 95% ethanol) 320 mμ (ε 43,500), (in 90% ethanol, 0·5N in HCl) 320 mμ (ε 44,000), (in 85% ethanol, N/20 in KOH) 303 mμ (ε 19,200), $\nu_{max.}$ (supercooled film) 3200, 1630, and 1550 cm.$^{-1}$, pK'_a 12·1 (in water).

The *picrate* formed yellow needles (from ethanol), m. p. 189° (Found: C, 53·2; H, 6·1; N, 15·6. $C_{20}H_{27}O_7N_5$ requires C, 53·4; H, 6·1; N, 15·6%).

The base (80 mg.) in methanol (3 ml.) was added to a solution of cobalt nitrate (200 mg.) in aqueous ammonia [1 ml. (*d* 0·880) + 5 ml. of water]. The yellow precipitate formed was extracted with methylene chloride, and the methylene chloride evaporated to give a yellow solid. Purification of this by recrystallisation from ethereal solution by addition of methanol gave the *cobalt complex* as orange prisms, m. p. 137° (Found: C, 67·6; H, 9·7; N, 11·0. $C_{28}H_{46}N_4Co$ requires C, 67·6; H, 9·3; N, 11·3%), $\lambda_{max.}$ (in *cyclo*hexane) 271 (ε 10,800), 324 (ε 29,400), and 431 mμ (ε 1600). A copper complex was readily obtained in a similar manner but this, a deep blue gum, could not be obtained crystalline. Both complexes were readily soluble in low-boiling light petroleum.

The toluene-*p*-sulphonyl derivative was obtained from the base (0·5 g.) by the action of toluene-*p*-sulphonyl chloride (0·5 g.) and triethylamine (0·5 ml.) in benzene (5 ml.). It crystallised from light petroleum in large colourless prisms (0·6 g.), shown by comparison of infrared spectra and by m. p. and mixed m. p. (142°) to be identical with the toluene-*p*-sulphonyl base previously obtained directly by the action of toluene-*p*-sulphonyl chloride and triethylamine on the bishydroxylamine (see above).

Ozonolysis of Toluene-p-*sulphonyl Derivative* (XVI).—This compound (0·25 g.) was dissolved in a mixture of glacial acetic acid (10 ml.) and ethyl acetate (5 ml.), and a stream of 3% ozonised oxygen was passed through the solution for 20 min. at 0°. Water (15 ml.) and zinc dust (0·5 g.) were added, and the solution was shaken at room temperature for 1 hr. After filtration the filtrate was evaporated to dryness below 60°, and water (10 ml.) added. The crystalline precipitate which separated was recrystallised from methylene chloride–light petroleum to give colourless platelets of 4 : 4-*dimethyl*-1-*toluene*-p-*sulphonylpyrrolid*-2-*one* (0·14 g.), m. p. 129° (Found: C, 58·2; H, 6·5; N, 5·3. $C_{13}H_{17}O_3NS$ requires C, 58·4; H, 6·4; N, 5·2%), $\nu_{max.}$ (mull) 1734, 1730, 1595, 1488, 1360, 1166, and 1160 cm.$^{-1}$.

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The above pyrrolidone (0·1 g.) was heated with a solution of potassium hydroxide (0·2 g.) in 50% aqueous ethanol (3 ml.) for 30 min. Acidification and extraction with ether yielded ββ-dimethyl-γ-toluene-*p*-sulphonamidobutyric acid as needles (from ether–low-boiling light petroleum), m. p. 148°, undepressed in admixture with an authentic specimen [9] (Found: C, 54·7; H, 6·9; N, 4·9. Calc. for $C_{13}H_{19}O_4NS$: C, 54·7; H, 6·7; N, 4·9%), $\nu_{max.}$ (mull) 3270, 2700, 1600, 1498, 1310, and 1153 cm.$^{-1}$.

We are indebted to the D.S.I.R. for a Research Studentship (I. O. S.) and the Royal Commissioners for the Exhibition of 1851 for an Overseas Scholarship (R. F. C. B.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, January 20th,* 1959.]

[9] Brown, Clark, and Todd, preceding paper.

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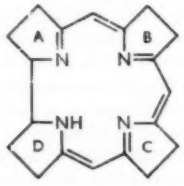
427. *Experiments towards the Synthesis of Corrins. Part VI.* The Dimerisation of* Δ^1*-Pyrroline* 1*-Oxides to* 2-(1′*-Hydroxypyrrolidin-*2′*-yl*)-Δ^1*-pyrroline* 1*-Oxides.*

By R. F. C. BROWN, V. M. CLARK, M. LAMCHEN, and SIR ALEXANDER TODD.

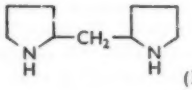
Under certain conditions, sodamide in liquid ammonia catalyses the dimerisation of Δ^1-pyrroline 1-oxides to 2 : 2′-dipyrrolidinyl derivatives. In the case of 5 : 5-dimethyl-Δ^1-pyrroline 1-oxide a degradative proof of structure of the dimer is presented.

THE corrin nucleus (I), upon which the macrocyclic component of the vitamin B_{12} chromophore [1] is based, is distinguished from the closely related porphyrins not only by the difference in oxidation level but also by the absence of a *meso*-carbon atom linking rings A and D. In exploring possible synthetic routes to the corrins we have therefore examined methods for the elaboration of intermediates related to 2 : 2′-bipyrrolidinyl (II), in addition to those based on dipyrrolidin-2-ylmethane (III). Derivatives of the latter formed the subject of the preceding paper in which the base-catalysed aldol-type reactions of various Δ^1-pyrroline 1-oxides (IV) were recorded.



(I)

(II)



(III)

The nitrone group (V), although capable of undergoing nucleophilic addition at the carbon atom,[2] might also be expected to exhibit electrophilic reactivity at that site as expressed by the canonical form (VI); indeed, the *N*-oxide linkage in pyridine 1-oxide is highly polarisable in both directions [3] and *electrophilic* substitution in the 4-position of pyridine oxide occurs readily.[4] Moreover, in the aliphatic series, the anion of nitromethane (V; R = H, R′ = O$^-$) dimerises by an addition equivalent to that of (V) to (VI) to yield, ultimately, nitroacetic acid; [5] and the adduct (V; R = H, R′ = Ph) of formaldehyde and

* Part V, preceding paper.

[1] Bonnett, Cannon, Clark, Johnson, Parker, Lester Smith, and Todd, *J.*, 1957, 1158, and references therein.

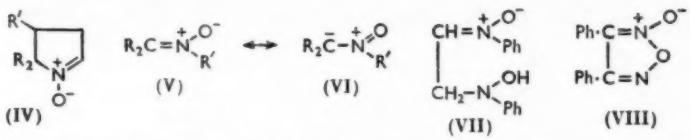
[2] Bonnett, Brown, Clark, Sutherland, and Todd, Part II, *J.*, 1959, 2094.

[3] Jaffé, *J. Amer. Chem. Soc.*, 1954, **76**, 3527; Katritzky, Randall, and Sutton, *J.*, 1957, 1769.

[4] Ochiai, *J. Org. Chem.*, 1953, **18**, 534; den Hertog, van Ammers, and Schukking, *Rec. Trav. chim.*, 1955, **74**, 1171.

[5] Steinkopf, *Ber.*, 1909, **42**, 3925.

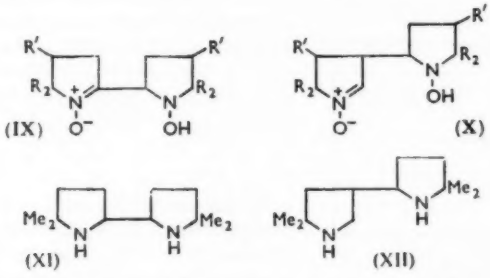
phenylhydroxylamine can only be isolated as an oxidation product of its dimer (VII).[6] The related nitrile oxide, Ph·C≡⁺N·O⁻, also dimerises in neutral or alkaline solution forming the furoxan derivative (VIII).[7]



(IV) (V) (VI) (VII) (VIII)

Irradiation of a Δ^1-pyrroline 1-oxide (IV; R = Me, R′ = H) did not lead to any dimeric product but gave instead the oxaziran;[8] however, treatment with sodamide in liquid ammonia yielded a compound (IX; R = Me, R′ = H) in which a 2 : 2′-linkage has been established: (IX) is then the direct analogue of (VII).

Earlier work on the action of bases on the Δ^1-pyrroline 1-oxides had shown them to undergo aldol-type reactions (preceding paper) and with the oxide (IV; R = R′ = Me) the action of triphenylmethylsodium gave rise to the bi-compound (X; R = R′ = Me). When sodamide in liquid ammonia was used an isomeric product was obtained whose infrared spectrum exhibited bands at 3170 and 1603 cm.$^{-1}$, indicating the presence of a hydroxyamino- and a nitrone group, though the position of the longer-wavelength band suggested a 2-substituted nitrone (cf. IX) rather than the unsubstituted system (X).[2] Aerial oxidation of this isomeric product in the presence of cuprammonium ion gave a dinitrone different from that obtained under similar conditions from the bi-compound (X; R = R′ = Me). As the 4-methyl group (R′ in IV) might have been the cause of isomerism attention was turned to 5 : 5-dimethyl-Δ^1-pyrroline 1-oxide (IV; R = Me, R′ = H): treatment with triphenylmethylsodium or with sodamide in liquid ammonia again gave isomeric products, each product being shown to be a nitrone-hydroxylamine on the basis of ultraviolet and infrared spectral evidence and its ability to reduce the triphenyltetrazolium chloride reagent.[9] The triphenylmethylsodium product exhibited an infrared band at 1575 cm.$^{-1}$ indicative of an unsubstituted nitrone, whilst the sodamide product absorbed at 1611 cm.$^{-1}$ as expected of a 2-substituted nitrone. Oxidation of each product either aerially in the presence of cuprammonium ion or by potassium ferricyanide[10] gave the corresponding dinitrone: the triphenylmethylsodium product then

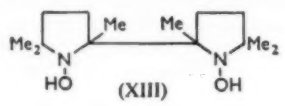


(IX) (X) (XI) (XII)

showed infrared bands at 1603 and 1570 cm.$^{-1}$ to be expected of an unsubstituted and a 2-substituted nitrone whilst the sodamide product exhibited a pronounced bathochromic shift to 1509 and 1503 cm.$^{-1}$ suggestive of an α-dinitrone system $^{-}O\cdot N^{+}{=}C\cdot C{=}^{+}N\cdot O^{-}$. The ultraviolet spectra showed analogous changes: thus, the triphenylmethylsodium product

[6] Kalle and Co., D.R.-P. 87972 (Friedländer, 1894/97, **4**, 49); von Pechmann, *Ber.*, 1897, **30**, 2461; Bamberger, *Ber.*, 1900, **33**, 941; Hellmann and Teichmann, *Chem. Ber.*, 1956, **89**, 1134.
[7] Werner and Buss, *Ber.*, 1894, **27**, 2193; Wieland and Semper, *Ber.*, 1906, **39**, 2522.
[8] Bonnett, Clark, and Todd, Part III, *J.*, 1959, 2102.
[9] Rogers, *J.*, 1955, 769; Snow, *J.*, 1954, 2588.
[10] Thesing and Mayer, *Annalen*, 1957, **609**, 46.

had maximum absorption at 237 mμ (ε 16,500) as expected of two isolated nitrone functions, whereas for the α-dinitrone system of the sodamide product it was at 331 mμ (ε 18,500).



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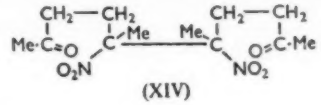
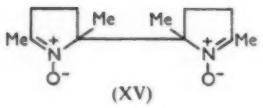
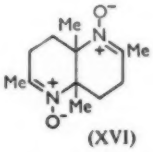


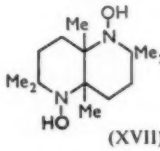
(XIV)



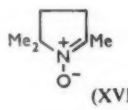
(XV)



(XVI)



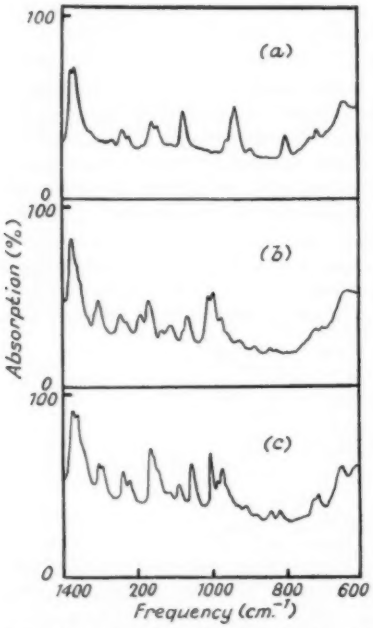
(XVII)



(XVIII)

The nuclear magnetic resonance spectra were complex, but only the nitrone-hydroxylamine dimer from the triphenylmethylsodium reaction showed any evidence of a uniquely situated hydrogen atom.

On the basis of this evidence we assign structure (IX; R = Me, R′ = H) to the sodamide product, and (X; R = Me, R′ = H) to the triphenylmethylsodium product. The assignment (IX) is confirmed by the reactions described below.



Infrared spectra of the bishydroxylamines (a) of B*, *structure* (XVII), *(b) of structure* (XIII) *derived from* (IX), *and (c) of structure* A*, (XIII) *derived from* (XV).

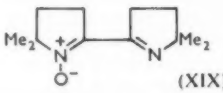
Reduction of the products (IX and X; R = Me, R′ = H) with aqueous sodium borohydride gave the bishydroxylamines, further reduction of which by zinc and hydrochloric acid gave the 2 : 2′-bipyrrolidinyl (XI) and the 2 : 3′-bipyrrolidinyl (XII). As expected, electrometric titration of the former disclosed two groups of different basicity (pK_{a1} 6·95; pK_{a2} 10·3), whereas the latter gave a single value (pK_a 9·2).

Addition of methylmagnesium iodide to the α-dinitrone derived from the 2 : 2′-bi-compound (IX; R = Me, R′ = H) gave the bishydroxylamine (XIII), almost certainly as the racemic rather than the *meso*-product. Oxidation of 5-nitrohexan-2-one with ammonium persulphate[11] gave 5 : 6-dimethyl-5 : 6-dinitrodecane-2 : 9-dione (XIV) whose reduction with zinc dust and ammonium chloride [2] gave a mixture of two nitrones, A, m. p. 150°, and B, m. p. 160—170°, one being (XV) and the other (XVI); addition of methylmagnesium iodide to each gave the corresponding bishydroxylamine A* and B* (presumably XIII and XVII). Neither was identical with the isomer obtained from the α-nitrone corresponding to (IX; R = Me, R′ = H). The oxidative dimerisation to give the dinitro-diketone (XIV) would presumably give the *meso*-product and hence the bishydroxylamine (XIII) derived from it by way of the nitrone (XV) would be *meso* whereas the isomer (XIII) derived from our dimerisation product (IX) would be the racemic isomer. The infrared spectra of A* and of (XIII) derived from (IX) were closely similar,

[11] Shechter and Kaplan, *J. Amer. Chem. Soc.*, 1953, **75**, 3980.

each differing somewhat in the fingerprint region from that of B* (see Figure). On this basis we assign structure (XIII) to A* and (XVII) to B*. On aerial oxidation both isomers (XIII) underwent cleavage to yield the same nitrone (XVIII),[2] this reaction being formally analogous to the cleavage of α-glycols by sodium metaperiodate. Aerial oxidation of (XVII) also gave the mononitrone (XVIII).

The function of the sodamide in the dimerisation of the pyrroline oxides (IV) to (IX) is uncertain. On occasion the use of sodamide gives aldol-type products [12] and in the present instance, with the compound (IV; R = Me, R′ = H), a change of solvent from liquid ammonia to triethylamine led from the exclusive formation of the 2 : 2′-compound (IX; R = Me, R′ = H) to the concurrent formation of some of the 2 : 3′-compound (X; R = Me, R′ = H). In both solvents the nitrone-hydroxylamine (IX; R = Me, R′ = H) underwent, in part, the loss of the elements of water, the nitrone-pyrroline (XIX) being also isolated. The direct linkage of aldehydic carbon atoms under basic conditions has been observed in the conversion of hydrobenzamide into amarin in the presence of potassamide,[13] and the removal of the aldehydic hydrogen atom under such conditions occurs in the formation of nitriles from *O*-esters of aromatic *anti*-aldoximes.[14] Whether or not the rôle of sodamide in the dimerisation of the nitrone (IV) to (IX) is proton-abstraction has yet to be determined.


(XIX)

Experimental

Dimerisation of 4 : 5 : 5-*Trimethyl*-Δ¹-*pyrroline* 1-*Oxide with Sodamide in Liquid Ammonia.*—The pyrroline oxide (12·7 g.) in liquid ammonia (50 ml.) was added to a solution of sodamide (from 4·6 g. of sodium) in liquid ammonia (300 ml.). The solution was left overnight in a well-insulated flask, then excess of sodamide was decomposed by adding first ammonium chloride (10 g.), then water (125 ml.). After evaporation of ammonia, the aqueous solution was filtered and extracted with chloroform (4 × 50 ml.). Evaporation of the dried (Na_2SO_4) chloroform extract and recrystallisation of the residue from chloroform–light petroleum gave the 2 : 2′-dimer, 2-(1′-*hydroxy*-4′ : 5′ : 5′-*trimethylpyrrolidin*-2′-*yl*)-4 : 5 : 5-*trimethyl*-Δ¹-*pyrroline* 1-*oxide* (IX; R = R′ = Me) (3·6 g., 28%) as colourless rods, m. p. 176—177° (Found: C, 66·3; H, 10·1; N, 11·2. $C_{14}H_{26}O_2N_2$ requires C, 66·1; H, 10·3; N, 11·0%), $\lambda_{max.}$ (in 95% ethanol) 233 mμ (ε 13,400), $\nu_{max.}$ (mull) 3170, 1603 cm.⁻¹.

Oxidation of 2 : 2′-*Dimer.*—The above dimer (0·5 g.) was dissolved in water (100 ml.) and ammonia (5 ml.; *d* 0·880) containing copper sulphate (50 mg.) and oxidised by passing a stream of air through the solution for 3 hr. The product was extracted with chloroform (3 × 25 ml.), and the crude solid obtained on evaporation of the chloroform extract was recrystallised from chloroform–low-boiling light petroleum to give a dinitrone, 4 : 5 : 5 : 4′ : 5′ : 5′-*hexamethyl*-*bi*-Δ¹-*pyrrolin*-2-*yl* 1 : 1′-*dioxide*, as colourless rods, m. p. 160° (Found: C, 66·9; H, 10·0; N, 11·4. $C_{14}H_{24}O_2N_2$ requires C, 66·7; H, 9·5; N, 11·1%), $\lambda_{max.}$ (in ethanol) 332 mμ (ε 9100), $\nu_{max.}$ (mull) 1504 cm.⁻¹.

Dimerisation of 5 : 5-*Dimethyl*-Δ¹-*pyrroline* 1-*Oxide with Sodamide in Liquid Ammonia.*—The pyrroline oxide (10·0 g.) was treated with sodamide (from 2·0 g. of sodium) in liquid ammonia (300 ml.) as described for the 4 : 5 : 5-trimethyl compound. After addition of ammonium chloride and water to the reaction mixture and evaporation of ammonia, the aqueous solution was extracted with chloroform. Evaporation of the chloroform extract gave a thick oil which crystallised when stirred with light petroleum. Recrystallisation from chloroform–light petroleum gave colourless needles of the 2 : 2′-dimer, 2-(1′-*hydroxy*-5′ : 5′-*dimethylpyrrolidin*-2′-*yl*)-5 : 5-*dimethyl*-Δ¹-*pyrroline* 1-*oxide* (IX; R = Me, R′ = H) (4·9 g., 49%), m. p. 177° (Found: C, 63·5; H, 9·9; N, 12·6. $C_{12}H_{22}O_2N_2$ requires C, 63·8; H, 9·7; N, 12·4%), $\lambda_{max.}$ (in 95% ethanol) 235 mμ (ε 10,500), $\nu_{max.}$ (mull) 3190, 1611 cm.⁻¹.

[12] Brown, Clark, Sutherland, and Todd, preceding paper.
[13] Strain, *J. Amer. Chem. Soc.*, 1927, **49**, 1558.
[14] Vermillion and Hauser, *J. Org. Chem.*, 1941, **6**, 507; Hauser and Hoffenberg, *ibid.*, 1955, **20**, 1535.

XUM

In experiments using a larger proportion of sodamide (from 4·6 g. of sodium) the pyrroline oxide (10 g.) gave none of the above 2 : 2′-nitrone-hydroxylamine dimer, but instead the nitrone-pyrroline, 5 : 5 : 5′ : 5′-*tetramethyl*-2 : 2′-*bi*-Δ^1-*pyrrolinyl* 1-*oxide* (XIX) was obtained in 10—20% yield. After sublimation at 90°/1 mm. and crystallisation from low-boiling light petroleum it formed colourless plates, m. p. 83° (Found: C, 69·4; H, 10·0; N, 13·5. $C_{12}H_{20}ON_2$ requires C, 69·2; H, 9·6; N, 13·5%), $\lambda_{max.}$ (in 95% ethanol) 224 and 285 mμ (ε 2100 and 11,100), $\nu_{max.}$ (mull) 1568 and 1542 cm.$^{-1}$.

Oxidation of 2 : 2′-*Dimer* (IX; R = Me, R′ = H).—Aerial oxidation of the above dimer (1·0 g.) in water (50 ml.) and ammonia (5 ml.; *d* 0·88) containing copper sulphate (0·2 g.) afforded 5 : 5 : 5′ : 5′-*tetramethyl*-2 : 2′-*bi*-Δ^1-*pyrrolinyl* 1 : 1′-*dioxide* as colourless plates (from chloroform–light petroleum) (0·9 g.), m. p. 162° (Found: C, 64·0; H, 9·3; N, 12·3. $C_{12}H_{20}O_2N_2$ requires C, 64·2; H, 8·9; N, 12·5%), $\lambda_{max.}$ (in 95% ethanol), 250—254 (ε 3200) and 331 mμ (ε 18,500), $\nu_{max.}$ (in chloroform) 1509, 1503 cm.$^{-1}$.

Reduction of this dinitrone (0·1 g.) with sodium borohydride (0·1 g.) in water (2 ml.) gave the bishydroxylamine 1 : 1′-*dihydroxy*-5 : 5 : 5′ : 5′-*tetramethyl*-2 : 2′-*bipyrrolidinyl* (0·07 g.) as colourless needles, m. p. 163° (Found: C, 62·9; H, 10·2; N, 12·6. $C_{12}H_{24}O_2N_2$ requires C, 63·1; H, 10·5; N, 12·3%), $\nu_{max.}$ (mull) 3260 cm.$^{-1}$.

Borohydride Reduction of 2 : 2′-*Dimer* (IX; R = Me, R′ = H).—The dimer (1·0 g.) and sodium borohydride (0·7 g.) were dissolved in water (15 ml.) and the solution was left at room temperature for 48 hr. The solid which had crystallised was collected, the filtrate was extracted with ether, and the solid and the product of ether-extraction were combined. Recrystallisation from ethanol gave the bishydroxylamine, previously obtained by reduction of the dinitrone identified by its m. p., mixed m. p. 163°, and by comparison of infrared spectra.

5 : 5 : 5′ : 5′-*Tetramethyl*-2 : 2′-*bipyrrolidinyl* (XI).—The above bishydroxylamine (1·75 g.) was treated in 20% w/v aqueous hydrochloric acid (10 ml.) with zinc dust (8 g.) in portions with shaking during 15 min., concentrated hydrochloric acid being added as necessary to dissolve the excess of zinc. The solution was filtered, made alkaline with ammonia, and extracted with chloroform. Evaporation of the dried (Na_2SO_4) chloroform extract gave the crude *bipyrrolidinyl* as a viscous, extremely hygroscopic oil (1·35 g., 90%) (Found: equiv., 108, by electrometric titration. $C_{12}H_{24}N_2$ requires equiv., 98). The oil had $pK_{a1} = 6·95$ and $pK_{a2} = 10·3$. For analysis the product was converted into its *dipicrate* which crystallised from aqueous ethanol as yellow needles, m. p. 267° (Found: C, 44·0; H, 4·5; N, 16·5. $C_{12}H_{24}N_2,2C_6H_3O_7N_3$ requires C, 44·0; H, 4·6; N, 17·1%).

Dimerisation of 5 : 5-*Dimethyl*-Δ^1-*pyrroline* 1-*Oxide with Ethereal Triphenylmethylsodium.*—A solution of triphenylmethylsodium, prepared from triphenylmethyl chloride (90 g.) and 1·2% sodium amalgam (1250 g.) in ether (1500 ml.), was added to a solution of the pyrroline oxide (35 g.) in ether (100 ml.). The mixture was left at room temperature for 48 hr., evaporated to 700 ml., and extracted with 5N-hydrochloric acid (5 × 50 ml.). The acidic extract was washed with ether, made alkaline by addition of excess of ammonia, and extracted with chloroform (6 × 40 ml.). Evaporation of the chloroform yielded a crystalline mass (*ca.* 20 g.), which was washed with ether and recrystallised from the same solvent, to give the 2 : 3′-*dimer* (X; R = Me, R′ = H) (13 g., 37%), m. p. 152—153° (Found: C, 63·6; H, 10·0; N, 12·6. $C_{12}H_{22}O_2N_2$ requires C, 63·8; H, 9·7; N, 12·4%), $\nu_{max.}$ (mull) 1576 cm.$^{-1}$.

Oxidation of 2 : 3′-*Dimer.*—A solution of potassium ferricyanide (5 g.) in water (15 ml.) was added dropwise to a stirred solution of the above 2 : 3′-dimer (1·0 g.) and potassium hydroxide (1·4 g.) in water (10 ml.) at room temperature. The solution was left overnight and then continuously extracted with chloroform. The dried (Na_2SO_4) chloroform extract was evaporated and the residue recrystallised from chloroform–ether to give 5 : 5 : 5′ : 5′-*tetramethyl*-2 : 3′-*bi*-Δ^1-*pyrrolinyl* 1 : 1′-*dioxide* as colourless hygroscopic crystals, m. p. 140° (Found: C, 59·9; H, 8·7; N, 11·4. $C_{12}H_{20}O_2N_2,H_2O$ requires C, 59·5; H, 9·1; N, 11·6%), $\lambda_{max.}$ (in 95% ethanol) 237 mμ (ε 16,500), $\nu_{max.}$ (in chloroform) 1603, 1570 cm.$^{-1}$.

Reduction of the 2 : 3′-*Dimer* (X; R = Me, R′ = H) *with Sodium Borohydride.*—Sodium borohydride (1 g.) was added to a solution of (X; R = Me, R′ = H) (1 g.) in water (5 ml.) and set aside for 48 hr. The mixture was filtered, the filtrate extracted with chloroform, and the extract dried (Na_2SO_4) and evaporated. The white crystalline residue of 1 : 1′-*dihydroxy*-5 : 5 : 5′ : 5′-*tetramethyl*-2 : 3′-*bipyrrolidinyl* was recrystallised from ether–light petroleum and then had m. p. 132—133° (Found: C, 62·9; H, 11·0; N, 12·4. $C_{12}H_{24}O_2N_2$ requires C, 63·1; H, 10·5; N, 12·3%).

XUM

5 : 5 : 5′ : 5′-*Tetramethyl*-2 : 3′-*bipyrrolidinyl* (XII).—To the preceding bishydroxylamine (0·5 g.) in 20% w/v hydrochloric acid (10 ml.) zinc dust (3 g.) was added with shaking. After 40 hr. some zinc was still undissolved, so concentrated hydrochloric acid (5 ml.) was added, and the mixture heated on the steam-bath for 4 hr., cooled, and filtered. The filtrate was made strongly alkaline with sodium hydroxide and extracted with chloroform, and the extract dried (Na_2SO_4) and evaporated. The bipyrrolidinyl remained as a colourless viscous oil (0·36 g., 83%) which was purified by short-path distillation. It was extremely hygroscopic and in air gave a *dihydrate*, m. p. 38° (Found: C, 62·3; H, 12·5; N, 12·0%; equiv., 116. $C_{12}H_{24}N_2,2H_2O$ requires C, 62·0; H, 12·1; N, 12·1%; equiv., 116). The infrared spectrum of the dihydrate had bands corresponding both to OH and NH groupings; the base had a single pK_a 9·2.

Dimerisation of 5 : 5-*Dimethyl*-Δ^1-*pyrroline* 1-*Oxide with Sodamide in Triethylamine*.—The pyrroline oxide (9·0 g.) was added to a suspension of sodamide (1·5 g.) in triethylamine (30 ml.). The mixture was stirred at room temperature for 18 hr., water (5 ml.) added, and the triethylamine evaporated. The residue was dissolved in water (15 ml.), and the solution extracted with chloroform (5 × 30 ml.). The dried ($MgSO_4$) chloroform extract was evaporated to an oil, which crystallised when stirred with pentane. Recrystallisation from light petroleum containing a little chloroform gave the 2 : 3′-dimer (X) (2·2 g., 24%), shown by comparison of infrared spectra and by the m. p. and mixed m. p. (152—153°) to be identical with that formed by the action of triphenylmethylsodium.

The pentane mother-liquors from the crystallisation of this compound were chromatographed on alumina (2 × 20 cm.), and the column was eluted with benzene–chloroform (1 : 1). Evaporation of the eluate yielded a solid which on sublimation at 90°/1 mm. gave the 2 : 2′-nitronepyrroline (XIX) (1·5 g., 18%), identified by the m. p. and mixed m. p. (82—83°) and by comparison of its infrared spectrum with that of the product formed in the presence of excess of sodamide.

1 : 1′-*Dihydroxy*-2 : 5 : 5 : 2′ : 5′ ; 5′-*hexamethyl*-2 : 2′-*bipyrrolidinyl* (XIII).—The dinitrone corresponding to (IX; R = Me, R′ = H) (2·2 g.) in benzene (100 ml.) was added dropwise to methylmagnesium iodide (from 2·0 g. of magnesium) in ether (150 ml.) under reflux. The clear solution was heated for 2 hr., then cooled and excess of Grignard reagent decomposed by aqueous ammonium chloride (10 g. in 100 ml.). The organic layer was separated and evaporated under reduced pressure. The residue was distributed between water (50 ml.) and ether (50 ml.), and the ethereal layer evaporated. Recrystallisation of the residue from aqueous methanol gave the *bishydroxylamine* (XIII) (0·4 g.) as colourless leaflets, m. p. 122° (Found: C, 65·6; H, 11·3; N, 10·7. $C_{14}H_{28}O_2N_2$ requires C, 65·6; H, 11·0; N, 10·9%), $\nu_{max.}$ (mull) 3400 cm.$^{-1}$.

Oxidative Fission of Bishydroxylamine (XIII).—The above bishydroxylamine (0·28 g.) was dissolved in 50% aqueous methanol (50 ml.), a solution of copper sulphate (20 mg.) in ammonia (2 ml.; *d* 0·880) added, and air bubbled through the solution for 2 hr. Evaporation below 60° gave a syrup, and this was dissolved in methylene chloride (20 ml.). The dried (K_2CO_3) solution was evaporated, and the residue treated with a slight excess of ethanolic picric acid. The precipitate recrystallised from ethanol as lemon-yellow needles (0·1 g.) of 2 : 5 : 5-trimethyl-Δ^1-pyrroline 1-oxide picrate, identified by comparison of infrared spectra and by its m. p. and mixed m. p. (98° [2]) (Found: C, 44·3; H, 4·7; N, 15·3. Calc. for $C_{13}H_{16}O_8N_4$: C, 43·8; H, 4·5; N, 15·7%).

Oxidative Dimerisation of 5-*Nitrohexan*-2-*one*.—A solution of the nitrohexanone [15] (120 g.) in ethanol (80 ml.) and 3N-aqueous sodium hydroxide (250 ml.) was stirred and cooled at 0—5° during dropwise addition of an ice-cold solution of ammonium persulphate (195 g.) and sodium acetate (88 g.) in water (400 ml.). Separation of the crystalline product was complete at 0° overnight. It was washed with water and recrystallised from aqueous methanol as prisms (31 g., 26%) of 5 : 6-*dimethyl*-5 : 6-*dinitrodecane*-2 : 9-*dione*, m. p. 88° (Found: C, 50·1; H, 7·3; N, 9·6. $C_{12}H_{20}O_6N_2$ requires C, 50·0; H, 7·0; N, 9·7%), $\nu_{max.}$ (mull) 1720, 1547 cm.$^{-1}$.

Reduction of 5 : 6-*Dimethyl*-5 : 6-*dinitrodecane*-2 : 9-*dione*.—The dinitro-dione (7·0 g.), zinc dust (14 g.), and ammonium chloride (2 g.) were shaken together in 50% aqueous ethanol (120 ml.) at room temperature for 6 hr. The mixture was filtered and the filter cake washed with warm water (3 × 25 ml.). The combined filtrate and washings were evaporated below 60° to a syrup. This was dissolved in methylene chloride (50 ml.), and the dried (K_2CO_3) solution was passed through a short column of magnesium carbonate (5 g.), concentrated to 5 ml., and treated with ether (100 ml.). After 24 hr. the crystals which had separated were collected and

[15] Shechter, Ley, and Zeldin, *J. Amer. Chem. Soc.*, 1952, **74**, 3664.

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recrystallised from methylene chloride–ether, to give pinkish prisms (1·9 g.) of crude dinitrone B, m. p. 160—170° (decomp.). This could not be purified further by crystallisation.

The *dipicrate* was prepared in ethanol and recrystallised therefrom as pale yellow needles, m. p. 190° (Found: C, 42·5; H, 4·0; N, 16·5. $C_{24}H_{26}O_{16}N_8$ requires C, 42·2; H, 3·8; N, 16·4%). The pure *base B* (**3** : **4** : **4***a* : **7** : **8** : 8*a-hexahydro*-**2** : **4***a* : **6** : 8*a-tetramethyl*-**1** : **5**-*diazanaphthalene* **1** : **5**-*dioxide*) (XVI) was regenerated from the picrate by decomposition with aqueous lithium hydroxide and continuous extraction with methylene chloride; it crystallised from benzene–ether as hygroscopic prisms, m. p. 194° (Found: C, 64·3; H, 8·7; N, 12·5. $C_{12}H_{20}O_2N_2$ requires C, 64·3; H, 9·0; N, 12·5%), $\lambda_{max.}$ (in 95% ethanol) 234 mμ (ε 16,500), $\nu_{max.}$ 1611 cm.$^{-1}$.

The combined methylene chloride–ether mother liquors from the crystallisation of crude dinitrone B were evaporated to a gum which was treated in ethanol (10 ml.) with an excess of ethanolic picric acid. The crystals which separated recrystallised from ethanol to give *dinitrone* A *monopicrate* (1·15 g.) as yellow needles, m. p. 188° (Found: C, 47·7; H, 4·9; N, 15·1. $C_{18}H_{23}O_9N_5$ requires C, 47·7; H, 5·1; N, 15·5%). This picrate (1·0 g.) was passed in methylene chloride (50 ml.) through a column of alumina (25 g.). Pure *dinitrone A* (**2** : **5** : **2′** : 5′*-tetramethyl*-**5** : 5′*-bi*-Δ^1*-pyrrolinyl* **1** : **1′**-*dioxide*) (XV) was eluted with methylene chloride (300 ml.) and crystallised from methylene chloride–ether as colourless prisms (0·4 g.), m. p. 150° (Found: C, 64·0; H, 8·9; N, 12·5%), $\lambda_{max.}$ (in 95% ethanol) 231 mμ (ε 16,799), $\nu_{max.}$ (mull) 1603 cm.$^{-1}$.

Addition of Methylmagnesium Iodide to Dinitrones A *and* B, *and Oxidative Fission of Products.*—(*a*) Crude dinitrone B, m. p. 160—170° (decomp.) (0·67 g.), was treated with ethereal methylmagnesium iodide (from 0·6 g. of magnesium) as described in the analogous preparation of (XIII). The products were distributed between water (50 ml.) and ether (50 ml.), and the ethereal layer was evaporated. Recrystallisation of the residue from aqueous methanol gave the *bishydroxylamine B** (**1** : 5-*dihydroxy*-**2** : **2** : **4***a* : **6** : **6** : 8*a-hexamethyl*-**1** : **5**-*diazadecalin*) (80 mg.) as colourless plates, m. p. 164° (Found: C, 65·5; H, 10·8; N, 10·7. $C_{14}H_{28}O_2N_2$ requires C, 65·6; H, 11·0; N, 10·9%), $\nu_{max.}$ (mull) 3420 cm.$^{-1}$.

Aerial oxidation of this bishydroxylamine (80 mg.) in aqueous methanol containing ammonia and copper sulphate and isolation of the product as picrate yielded a crude picrate (52 mg.) having m. p. 92°. Repeated recrystallisation from ethanol finally gave lemon-yellow needles, m. p. 98°, identified by its m. p. and mixed m. p. and by comparison of infrared spectra as **2** : **5** : 5-trimethyl-Δ^1-pyrroline 1-oxide picrate.

(*b*) Dinitrone A (0·25 g.) was treated in the same way with methylmagnesium iodide (from 0·2 g. of magnesium). The bishydroxylamine, isolated as in (*a*), was recrystallised from the minimum volume of pentane. It underwent autoxidation very rapidly and two experiments failed because the product was autoxidised during working up. The most successful experiment gave the *bishydroxylamine A** (**1** : **1′**-*dihydroxy*-**2** : **5** : **5** : **2′** : **5′** : 5′*-hexamethyl*-**2** : **2′**-*bipyrrolidinyl* (20 mg.) as colourless needles, m. p. 102° (Found: C, 65·6; H, 10·8; N, 11·1%), $\nu_{max.}$ (mull) 3400 cm.$^{-1}$.

Aerial oxidation of bishydroxylamine A* (15 mg.) in the usual way and isolation of the product as its picrate yielded a small quantity of lemon-yellow needles, m. p. 96°, which did not depress the m. p. of **2** : **5** : 5-trimethyl-Δ^1-pyrroline 1-oxide picrate (98°).

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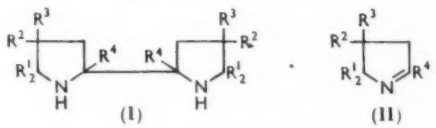
University Chemical Laboratory, Cambridge. [*Received, January 20th,* 1959.]

428. *Experiments towards the Synthesis of Corrins. Part VII.* The Reductive Dimerisation of a Δ^1-Pyrroline 1-Oxide. Oxidative Degradation of 2 : 2′- and 2 : 3′-Bipyrrolidinyl Derivatives.*

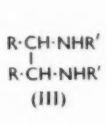
By V. M. Clark, B. Sklarz, and Sir Alexander Todd.

Sodium–potassium alloy in ethylene glycol dimethyl ether reduces 5 : 5-dimethyl-Δ^1-pyrroline 1-oxide to a 1 : 1′-dihydroxy-2 : 2′-dipyrrolidinyl. Oxidation by sodium metaperiodate readily distinguishes between the 2 : 2′- and 2 : 3′-dipyrrolidinyl series.

The 2 : 2′-dipyrrolidinyl system (I), parent of the A–D bicyclic component of the corrins, can be formally regarded as the product of the reductive dimerisation of the Δ^1-pyrroline (II), the relationship being analogous to that of a carbonyl compound and its corresponding pinacol. The reductive dimerisation of ketones to pinacols is readily accomplished by using a variety of reagents;[1-3] moreover, electrolytic methods[4] can give high yields. The acyloin reaction[5] might be regarded as a related example. However, application of such methods to azomethines with the object of generating 1 : 2-diamines has received little attention though Anselmino[6] has recorded the reductive dimerisation of benzylideneaniline to *N* : *N*′ : 1 : 2-tetraphenylethane-1 : 2-diamine (III; R = R′ = Ph) using aluminium amalgam in moist ether, and Thies and Schoenenberger[7] have obtained the related


(I)

(II)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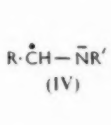
(IV)

product (III; R = Ph, R′ = Et) from benzylidene-ethylamine under the same conditions and by the action of *tert.*-butylmagnesium chloride in ether. The formation of compounds (III; R = Ph) is presumably facilitated by the stability of the intermediary benzyl-type radical-ion (IV; R = Ph), reduction of which by the addition of a further electron is slow, dimerisation supervening. Such stabilisation is absent in the aliphatic series and only one example of the reductive dimerisation of an aliphatic azomethine has been recorded, Picon[8] having obtained *NN*′-diethylbutane-2 : 3-diamine (III; R = Me, R′ = Et) from the action of sodium in liquid ammonia upon *N*-ethylidene-ethylamine. In our hands, sodium in liquid ammonia reduced benzylidene-ethylamine to *N*-ethylbenzylamine but was without action upon 2 : 4 : 4-trimethyl-Δ^1-pyrroline (II; R^1 = H, R^2 = R^3 = R^4 = Me), as was magnesium and mercuric chloride in dry benzene. Aluminium amalgam in moist ether reduced the Δ^1-pyrroline (II; R^1 = R^2 = Me, R^3 = R^4 = H) to the corresponding pyrrolidine.

The addition of the first electron to R·CH=NR′ gives the radical-ion (IV), addition of a second electron to which is facilitated by prior protonation of the *N*-atom, thereby preventing the formation of the dianion, R·$\bar{C}$H–$\bar{N}$R′, and giving instead R·$\bar{C}$H–NHR′. Absence of a proton source would be expected to favour the dimerisation of a radical-ion (IV) to

* Part VI, preceding paper.

[1] Squire, *J. Amer. Chem. Soc.*, 1951, **73**, 2586.
[2] Newman, *ibid.*, 1940, **62**, 1683.
[3] Gaertner, *J. Org. Chem.*, 1950, **15**, 1006.
[4] Allen, *J. Amer. Chem. Soc.*, 1951, **73**, 3503.
[5] Prelog, *Helv. Chim. Acta*, 1947, **30**, 1741; Stoll and Hulstkamp, *ibid.*, p. 1815.
[6] Anselmino, *Ber.*, 1908, **41**, 621.
[7] Thies and Schoenenberger, *Chem. Ber.*, 1956, **89**, 1918.
[8] Picon, *Compt. rend.*, 1922, **175**, 695.

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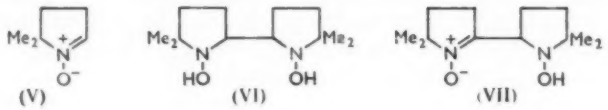
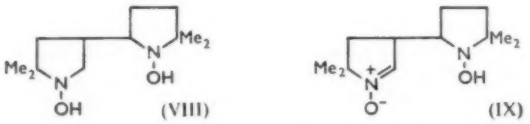
the dianion of (III) rather than its reduction to R·CH_2·NHR′. Wilkinson and his co-workers [9] have recently shown that liquid sodium–potassium alloys are soluble in ethylene glycol dimethyl ether and that such solutions convert benzyl chloride into dibenzyl and initiate polymerisation of isoprene, styrene, and acrylonitrile. When this aprotic reducing system was used the Δ^1-pyrrolines (II; $R^1 = R^2 = Me$, $R^3 = R^4 = H$; and $R^1 = H$, $R^2 = R^3 = R^4 = Me$) gave oils, and in the second case the Δ^1-pyrroline was partly recovered. However, the Δ^1-pyrroline 1-oxide (V) gave, in low yield, the bishydroxylamine (VI) identical with the product from borohydride reduction of the dimer (VII) obtained from (V) by the action of sodamide in liquid ammonia (preceding paper).

The structure of the nitrone-hydroxylamine (VII) had been previously established, but confirmation was sought in the oxidative degradation of the bishydroxyamine (VI), in particular, by the 1 : 2-glycol-splitting reagents, lead tetra-acetate and sodium metaperiodate. The cleavage of carbon–carbon bonds by both these reagents is not restricted to linked oxygenated carbon atoms, for lead tetra-acetate cleaves α-amino-alcohols [10] and α-amino-acids, and periodate [11] has been reported to oxidise ethylenediamine [12] and piperazine [13] with carbon–carbon bond-cleavage. In our hands lead tetra-acetate was


(V) (VI) (VII)


(VIII) (IX)

found to oxidise ethylenediamine in glacial acetic acid at 60° and, though no formaldehyde was detected, *N*-formylethylenediamine was isolated. The diamine (III; R = Ph, R′ = Et) consumed two mols. of the reagent, carbon–carbon cleavage occurring with the formation of two mols. of benzaldehyde, isolated as the 2 : 4-dinitrophenylhydrazone. However, 1 : 3-diaminopropane also reacted under the same conditions and although no product was isolated it was apparent that lead tetra-acetate was not sufficiently selective as a reagent to distinguish between the 2 : 2′-bipyrrolidinyl series (VI; VII) and the isomeric 2 : 3′-bipyrrolidinyl series (VIII; IX).

(X) (XI)

Sodium metaperiodate was found to oxidise ethylenediamine (one mole per mole) to formaldehyde (cf. ref. 12), whilst with 1 : 3-diaminopropane there was no reaction. The diamine (III; R = Ph, R′ = Et) was oxidised to a mixture of benzylidene-ethylamine and benzaldehyde, the uptake of periodate again being one mole per mole of diamine. Periodic acid itself also reacted with ethylenediamine and with the amine (III; R = Ph, R′ = Et) although only to a small extent; with 1 : 3-diaminopropane there was again no reaction. The suppression of oxidation of the 1 : 2-diamines under acidic conditions accords with

[9] Down, Lewis, Moore, and Wilkinson, *Proc. Chem. Soc.*, 1957, 209.
[10] Criegee, *Angew. Chem.*, 1940, **53**, 321; Leonard and Rebenstorf, *J. Amer. Chem. Soc.*, 1945, **67**, 49.
[11] Cf. McCasland and Smith, *ibid.*, 1951, **73**, 5164; Nicolet and Shinn, *ibid.*, 1939, **61**, 1615; Bragg and Hough, *J.*, 1958, 4050.
[12] Fleury, Courtois, and Grandchamp, *Bull. Soc. chim. France*, 1949, 88.
[13] Wickstrøm and Valseth, *Ann. Pharm. franç.*, 1954, **12**, 777.

McCasland and Smith's observations [11] on the aminocyclanols where the rates of oxidation were approximately proportional to the amount of unprotonated substrate.

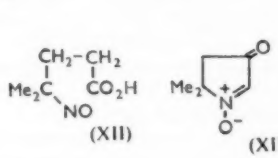
In the 2 : 2′-bipyrrolidinyl series, sodium metaperiodate oxidised the bishydroxylamine (VI) and the hydroxylamine-nitrone (VII) to the α-dinitrone (X), the consumption of periodate after 18 hr. at room temperature being 2·1 and 0·9 mole respectively. Considerably higher periodate absorption was observed in the 2 : 3′-linked series (VIII) and (IX) (see Table), oxidation beyond the β-dinitrone stage (XI) occurring, with the development of a bright blue colour: the β-dinitrone (XI) gave an immediate blue colour with periodate and during 12 hours the pH fell to 3 and a colourless crystalline product separated: analysis, spectra, and its blue melt are consistent with its being the dimer of 4-methyl-4-nitrosopentanoic acid (XII). Periodate oxidation of the bishydroxylamine (VIII) and nitrone-hydroxylamine (IX) gave the same nitroso-acid (XII) together with the keto-nitrone (XIII) isolated as its 2 : 4-dinitrophenylhydrazone, which was identical with that prepared from the parent nitrone (V) by oxidation with selenium dioxide.[14] This

Periodate uptake (mol.) by bipyrrolidinyl derivatives.

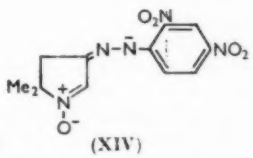
Substrate	After 18 hr.	After 42 hr.
2 : 2′-Series		
Bishydroxylamine (VI)	2·1	2·8
Nitrone-hydroxylamine (VII)	0·9	0·98
α-Dinitrone (X)	0	0
2 : 3′-Series		
Bishydroxylamine (VIII) [a]	4·3	4·8 [b]
Nitrone-hydroxylamine (IX)	4·0	4·6
β-Dinitrone (XI)	2·3 [c]	2·8 [c]

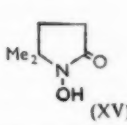
[a] In aqueous dioxan. [b] Unchanged after 96 hr. [c] Based on dihydrate.

2 : 4-dinitrophenylhydrazone gave a deep purple colour in alkaline solution due, presumably, to the anion (XIV). Oxidation of the hydroxamic acid, 1-hydroxy-5 : 5-dimethylpyrrolid-2-one (XV) also gave the nitroso-acid (XII) with the uptake of one mol. of periodate.

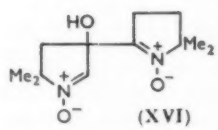

(XII)

(XIII)


(XIV)


(XV)

From the periodate consumption in the 2 : 2′-series and the isolation of the α-dinitrone (X) from both the bishydroxylamine (VI) and nitrone-hydroxylamine (VII) the first stage of oxidation is conversion of the secondary hydroxyamino-groups into nitrones; [15] in the 2 : 3′-series the initial reactions are similar. However, the 3′-carbon atom of the β-dinitrone (XI) is adjacent to two nitrone groups and periodate has been shown to oxidise activated methylene groups,[16] hydrogen being replaced by hydroxyl, the normal cleavage reaction then ensuing. The course of oxidation of the 2 : 3′-compound (XI) is consistent with oxidation to the 3′-hydroxy-derivative (XVI), cleavage of which gives the keto-nitrone (XIII) and the hydroxamic acid (XV), the latter being further oxidised to the nitroso-acid (XII).


(XVI)

Experimental

1 : 1′-*Dihydroxy*-5 : 5 : 5′ : 5′-*tetramethyl*-2 : 2′-*bipyrrolidinyl* (VI).—Freshly distilled 5 : 5-dimethyl-Δ¹-pyrroline 1-oxide (V) (5 g.) was added to a stirred suspension of sodium–potassium

[14] Cf. Brown, Clark, and Todd, *J.*, 1959, 2105.

[15] Cf. Utzinger and Regenass, *Helv. Chim. Acta*, 1954, **37**, 1892; Thesing and Mayer, *Annalen*, 1957, **609**, 46.

[16] Huebner, Ames, and Bubl, *J. Amer. Chem. Soc.*, 1946, **68**, 1621; Wolfrom and Bobbitt, *ibid.*, 1956, **78**, 2489.

alloy (25% Na; 1·5 g.) in anhydrous ethylene glycol dimethyl ether (150 ml.) which was cooled in an acetone–solid carbon dioxide bath and kept under oxygen-free nitrogen. The blue colour of the suspension was slowly discharged and excessive cooling of the alloy was avoided by removing the cooling-bath at intervals. After 4 hr., only a trace of alloy remained suspended in the yellowish-green solution and it was destroyed by cautiously adding ethanol (10 ml.). The solution was then evaporated under reduced pressure to a thick paste, and water (20 ml.) was added. Extraction with ether gave a sticky solid which was stirred with light petroleum, and the crystalline product (0·5 g.) collected and recrystallised from ethanol. The bishydroxyamine formed colourless needles, m. p. 163° (Found: C, 63·2; H, 10·9; N, 12·4. Calc. for $C_{12}H_{24}O_2N_2$: C, 63·1; H, 10·6; N, 12·3%). It showed no depression in m. p. when mixed with a specimen (m. p. 163°) prepared from the corresponding nitrone-hydroxylamine (VII) by reduction with borohydride.

Periodate Oxidation of Bipyrrolidinyl Derivatives (*cf. Table*).—(a) *Estimations.* In the case of the 2 : 2′-bipyrrolidinyl derivatives (VI, VII, X), a weighed amount (*ca.* 20 mg.) of the substance was added to sodium metaperiodate solution (0·09 g. in 10 ml.), and the mixture diluted to 100 ml. with water, giving a clear solution [it was necessary to use 20 ml. of dioxan to bring (VI) into solution]. Controls were also made up with and without dioxan and aliquot parts of the solutions were titrated after 18 and 42 hr. with 0·0109N-sodium arsenite.

The 2 : 3′-bipyrrolidinyl compounds (VIII, IX, XI) were similarly treated but 20 ml. of reagent solution were used in each case.

(b) *Preparative experiments*: (1) Oxidation of (VI) and (VII). The 2 : 2′-bishydroxylamine (VI) (0·1 g.) was dissolved in methanol (6 ml.), and sodium metaperiodate (200 mg. in 2 ml.). added. More water (6 ml.) was added to re-dissolve a slight precipitate, and the solution was set aside overnight. Methanol was then removed under reduced pressure, the aqueous solution extracted with chloroform (6 × 10 ml.), and the extract dried ($MgSO_4$) and evaporated; recrystallisation of the residue from chloroform–light petroleum gave the dioxide (X), identified by direct comparison with an authentic specimen (m. p., mixed m. p. and infrared spectrum). The same 2 : 2′-dinitrone was obtained by a similar oxidation of the nitrone-hydroxylamine (VII).

(2) Oxidation of 1-hydroxy-5 : 5-dimethylpyrrolid-2-one. When aqueous sodium metaperiodate (0·47 g. in 5 ml.) was added to 1-hydroxy-5 : 5-dimethylpyrrolid-2-one (0·25 g.) the solution at once became blue and a white precipitate formed. After 18 hr. the precipitate was collected and recrystallised first from water and then from chloroform. The colourless crystalline product, believed to be the dimeric form of *4-methyl-4-nitrosopentanoic acid* (XII), melted at 109—110° to a blue liquid (Found: C, 49·6; H, 7·6; N, 9·5. $C_6H_{11}O_3N$ requires C, 49·6; H, 7·6; N, 9·7%); its infrared spectrum showed a band at 1720 cm.$^{-1}$.

(3) Oxidation of the 2 : 3′-dinitrone (XI). On addition of aqueous sodium metaperiodate (0·57 g. in 4 ml.) to a solution of the dinitrone (0·135 g.) in water (1 ml.) the mixture at once became blue and after 2 hr. colourless crystals began to separate. After 18 hr. these were collected; they melted at 106—107°, giving a blue liquid. The recrystallised product was identical with that obtained as in (2) above (mixed m. p., infrared).

(4) Oxidation of (VIII) and (IX). The bishydroxylamine (VIII) (0·45 g.) in dioxan (5 ml.) was added to aqueous sodium metaperiodate (2 g. in 10 ml.). The solution became first blue, then green, and after 18 hr. it was concentrated to 2 ml. and extracted with chloroform. Evaporation of the dried extract gave an oil containing colourless crystals. A small amount of chloroform was added and the crystalline material collected. It had m. p. 107—110° to a blue liquid and the m. p. was undepressed in admixture with the nitroso-compound prepared as in (2) above.

The filtrate from the nitroso-compound was evaporated, and the dark oil dissolved in a little methanol and treated with 2 : 4-dinitrophenylhydrazine in methanolic sulphuric acid in the usual way. The crude 2 : 4-dinitrophenylhydrazone had m. p. 248°. The same two products were obtained by similar treatment of the nitrone-hydroxylamine (IX).

The above hydrazone, recrystallised first from chloroform–light petroleum, then from chloroform alone, formed orange needles, m. p. 256°, $\nu_{max.}$ 1538 cm.$^{-1}$, $\lambda_{max.}$ (in 95% ethanol) 385 (ε 32,500), 266 (ε 13,800) and 219 mμ (ε 13,300), $\lambda_{min.}$ 312 (ε 4930) and 250 mμ (ε 12,000). With aqueous sodium hydroxide the substance gave a purple colour. It was identified by direct comparison (m. p., mixed m. p., and infrared spectrum) as the 2 : 4-dinitrophenylhydrazone of 5 : 5-dimethyl-Δ^1-pyrrolin-3-one 1-oxide (XIII) (see below).

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Oxidation of 5 : 5-*Dimethyl*-Δ^1-*pyrroline* 1-*Oxide with Selenium Dioxide.*—The nitrone (V) (1 g.) in methanol (10 ml.) containing selenium dioxide (1 g.) was heated under reflux for 1½ hr. The suspension was cooled, filtered (Hyflo), and evaporated, and the residue taken up in water (15 ml.) and continuously extracted with ether for 24 hr. The dried (Na_2SO_4) extract was passed through a column of magnesium carbonate, then evaporated to a yellow oil which was treated in methanol (10 ml.) with 2 : 4-dinitrophenylhydrazine (1 g.) in 1 : 3 v/v aqueous methanol (20 ml.) containing concentrated sulphuric acid (2 ml.). 5 : 5-*Dimethyl*-Δ^1-*pyrrolin*-3-*one* 1-*oxide* 2 : 4-*dinitrophenylhydrazone* (XIII) separated; it had m. p. 255° after recrystallisation from ethyl acetate (Found: C, 46·7; H, 4·3; N, 22·3. $C_{12}H_{13}O_5N_5$ requires C, 46·9; H, 4·3; N, 22·8%).

We thank the D.S.I.R. for a Research Studentship (awarded to B. S.) and Professor G. Wilkinson for the use of laboratory facilities at the Imperial College of Science and Technology when carrying out reductions with sodium–potassium alloy.

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429. *Fatty Acids. Part VI.* The Oxygenated Acid present in* Camelina sativa *(Crantz.) Seed Oil.*

By F. D. GUNSTONE and L. J. MORRIS.

Evidence is presented for the occurrence of 15 : 16-epoxylinoleic acid in *C. sativa* seed oil.

CAMELINE oil, also known as dodder oil, German sesame oil, Leindotteröl, and Rullöl, is obtained from the seeds of *Camelina sativa* (Crantz.), syn. *Myagrum sativum* (Crantz.). This plant is widely dispersed through Europe and small amounts of the seed oil enter commerce. Recent chemical investigations of the oil have been reported by Swedish[1] and German workers[2,3] who in general agree about its composition. The saturated acids are accompanied by monoethenoid, linoleic, and linolenic acid, and as with other oils of the Cruciferae the monoethenoid acids include those of the C_{16}, C_{18}, C_{20}, and C_{22} series. von Mikusch also draws attention to the presence of an oxygenated acid which we have now further examined.

The oil was treated with acetic acid to hydrolyse any epoxide and, from the acids resulting on hydrolysis, concentrates of a dihydroxy-acid were isolated by urea-complex formation, partition, and chromatography. There was evidence of other hydroxy-acids but attention was directed mainly to the dihydroxy-acid obtained as a 55% and as a 75% concentrate, designated concentrate A and B respectively.

Concentrate A in the presence of palladium–charcoal took up 2 mols. of hydrogen and furnished a dihydroxystearic acid (II) (42% yield) different from the known 9 : 10- and 12 : 13-*threo*-dihydroxystearic acids of similar melting point. Concentrate B gave the same product (58%). Periodate oxidation of the hydrogenation product occurred smoothly and gave propionaldehyde and 14-formyltetradecanoic acid (III). The latter was recognised, after oxidation, as pentadecanedioic acid (IV) by comparison with an authentic sample prepared by Arndt–Eistert bishomologation[4] of tridecanedioic acid, itself obtained by oxidation of erucic acid. The hydrogenation product must therefore be the hitherto unknown (+)-15 : 16-dihydroxystearic acid (II) and in view of its melting point is probably a *threo*-isomer [cf. the values given by Huber[5] for the (±)-7 : 8- to -12 : 13-di-

* Part V, *J.*, 1957, 487.

[1] Holmberg and Sellmann, *Svensk Kem. Tidskr.*, 1952, **64**, 270; *Chem. Abs.*, 1953, **47**, 2514.
[2] von Mikusch, *Farbe und Lack*, 1952, **58**, 402; *Deutsche Farben-Zeitschrift*, 1952, 391.
[3] von Mikusch and Dylla, *J. Amer. Oil Chemists' Soc.*, 1954, **31**, 114.
[4] Cf. Walker, *J.*, 1940, 1304.
[5] Huber, *J. Amer. Chem. Soc.*, 1951, **73**, 2730.

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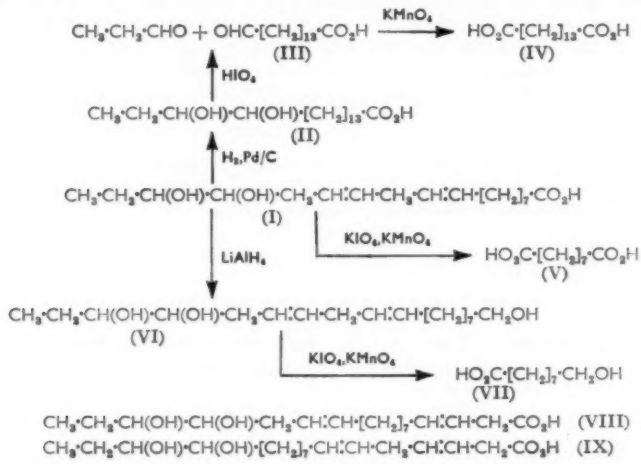
hydroxystearic acids). The relation between the melting point of this acid and of its methyl and ethyl esters (96°, 90°, and 74° respectively) differs somewhat from those in the corresponding (±)-9 : 10- (95°, 71°, and 60°) and (—)-12 : 13-series (95°, 68°, and 62°).



These experiments suggest that the acid probably contains two double bonds. The low absorption at 234 mμ before isomerisation by alkali and the greater value after isomerisation are indicative of the pentadiene system $-CH{:}CH{\cdot}CH_2{\cdot}CH{:}CH-$ familiar among natural unsaturated acids.[6] The extinction ($E^{1\%}_{1\,cm.}$) estimated to be 590 for the pure acid by extrapolation of values reported on p. 2130, is slightly lower than might have been expected from known octadecadienoic acids even after allowance for the increased molecular weight. Absence of absorption in the 10 μ region, associated with *trans*-olefinic groups, suggests that both unsaturated centres must have the *cis*-configuration.

The position of these unsaturated centres has been determined by oxidative degradation by the permanganate–periodate procedure of von Rudloff.[7] The unsaturated acid itself gave azelaic acid (V) which accords with structure (I) but would also result from structures (VIII) and (IX). The last two are less likely in view of the ultraviolet spectrum after isomerisation by alkali and would be novel for unsaturated acids of lipid origin.

A decision between these possibilities is made by labelling the carboxyl group and then oxidising in such a way as to retain the label in one of the oxidation products. This is generally done by esterification, or more satisfactorily, by extending the chain-length of the molecule by the Arndt–Eistert reaction.[8] However, in this investigation, the unsaturated acid (I) was reduced by lithium aluminium hydride to the unsaturated alcohol (VI), and this was oxidised by von Rudloff's method to 9-hydroxynonanoic acid, thereby confirming structure (I). The reaction was tested with oleyl alcohol which also provided a reference sample of the hydroxynonanoic acid.

These experiments show that concentrates of 15 : 16-dihydroxylinoleic acid are obtainable from cameline oil but do not indicate whether the compound is present as a glyceride in the original oil or as an epoxy-glyceride, or whether it is an artefact produced by oxidation, presumably of linolenic acid. It is considered to occur as an epoxy-glyceride for the

[6] Pitt and Morton, "Progress in the Chemistry of Fats and Other Lipids," Pergamon Press, London, 1957, Vol. IV, p. 228.

[7] von Rudloff, *J. Amer. Oil Chemists' Soc.*, 1956, **33**, 126; *Canad. J. Chem.*, 1955, **33**, 1714; 1956, **34**, 1413; Lemieux and von Rudloff, *ibid.*, 1955, **33**, 1701, 1710; Jones and Stolp, *J. Amer. Oil Chemists' Soc.*, 1958, **35**, 71.

[8] Whitcutt and Sutton, *Biochem. J.*, 1956, **63**, 469.

following reasons. (i) The 15 : 16-dihydroxystearic acid (II) shows a small but real optical activity whereas products resulting from atmospheric oxidation would be optically inactive. The dihydroxylinoleic acid (I) is also optically active but since this is not pure it cannot be used as a basis for argument. (ii) Gold [9] has recently concluded that autoxidation of *cis*-olefins affords *cis*- and *trans*-epoxides and thence *threo*- and *erythro*-glycols, whilst *trans*-olefins give only *trans*-epoxides and thence *erythro*-glycols. The higher-melting and less soluble *erythro*-glycols are more easily isolated and since only a *threo*-glycol was obtained in the present work it is unlikely to have resulted by autoxidation. (iii) Evidence in favour of the presence of an epoxide in the original oil is based on the infrared spectra of the neutral oil and of the mixed esters derived therefrom by acid-hydrolysis (which would open any epoxide ring). The spectra of cameline oil and its ester were compared with those of olive oil and its ester (as a control containing no epoxide), and with those of *Vernonia anthelmintica* seed oil and its ester (as a control containing 67% of epoxyoleic glycerides [10]). The region 2·6—3·3 μ was scanned since hydroxyl groups show an absorption band at 2·8 μ attributed to the O–H stretching vibration.[11] Olive oil showed slight absorption between 2·8 and 2·9 μ, possibly owing to autoxidation as the sample was not very fresh; the derived methyl esters showed an almost identical curve. With vernonia oil, on the other hand, there was very little absorption in this region, but very strong absorption with the methyl esters owing to the liberated glycol group. Cameline oil showed slight absorption in the 2·8—2·9 μ region but a very much larger absorption after conversion into the esters. This is taken as evidence that the diol group is formed at this stage, presumably from epoxides. Incidentally this provides a more sensitive method of detecting small amounts of epoxides than the quantitative methods involving reaction with excess of halogen acid.

This is now the third epoxy-acid to be reported in seed fats: 12 : 13-epoxyoleic acid (*Vernonia anthelmintica*,[10] *V. colorata*,[12] *Cephalocroton cordofanus*,[13] and *Hibiscus esculentus* [12]), 12 : 13-epoxylinoleic acid (*Camelina sativa*), and 9 : 10-epoxyoctadec-12-enoic acid (*Chrysanthemum coronarium* [14]). Four different plant families are included in this list and it seems that epoxy-acids are more widely distributed than has been recognised hitherto. Epoxyoleic and epoxylinoleic acids form a series and it is interesting to speculate on the possible natural occurrence of 9 : 10-epoxystearic acid which would complete the series. This would give rise to 9 : 10-dihydroxystearic acid and it is known that such an acid is present in castor oil. There is, however, no evidence that this is formed from an epoxide precursor [15] and, in addition, this natural dihydroxy-acid is of the *erythro*-series which would be derived, if at all, from the *trans*-epoxide whereas the natural epoxy-acids are *cis*-isomers, forming the *threo*-glycols.

Experimental

Fuller experimental details of some procedures are given in earlier papers by one of us.[10,13,16] Glycol values [16] are expressed as percentage of dihydroxylinoleic acid, except where otherwise stated.

Preparation of a Concentrate of the Unsaturated Dihydroxy-acid.—Cameline oil (32·5%) was obtained by extracting the crushed seeds with light petroleum (b. p. 40—60°). The oil (500 g.) was refluxed with acetic acid (2 l.) for 8 hr. (to hydrolyse any epoxides) and after removal of the acetic acid the mixed fatty acids were liberated by alkaline hydrolysis in the usual manner.

The mixed acids (471 g.), acetylated by treatment with boiling acetic anhydride, were dissolved in methanol (500 ml.) and added during half an hour to a hot mixture of urea (1·4 kg.)

[9] Gold, *J.*, 1958, 934.
[10] Gunstone, *J.*, 1954, 1611.
[11] Ahlers and McTaggart, *Analyst*, 1954, **79**, 70.
[12] Chisholm and Hopkins, *Canad. J. Chem.*, 1957, **35**, 358.
[13] Bharucha and Gunstone, *J. Sci. Food Agric.*, 1956, **7**, 606.
[14] Smith, Koch, and Wolff, *Chem. and Ind.*, 1959, 259.
[15] Gunstone and Sykes, unpublished observation.
[16] Bharucha and Gunstone, *J. Sci. Food Agric.*, 1955, **6**, 373.

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and methanol (1·8 l.). The mixture was kept at room temperature overnight, then filtered, and the filter-cake washed with cold methanol–urea solution. The acids (95·5 g.) which did not form a complex were removed from the filtrate by ether-extraction after dilution with water. (In a similar experiment, where the acetylated methyl esters were used, this fraction was shown to contain practically all the acetylated material.)

Hydroxy-compounds were further concentrated by partition between 80% methanol and light petroleum,[16] and the material in the methanol extract was hydrolysed and freed from unsaponifiable material, leaving the concentrate A (10·69 g., 2·3% of the mixed acids; glycol value 55%) (the petroleum extract contained 17·6% of the total acids by wt.).

After repetition of the partition, samples of the aqueous methanol extract were further purified by chromatography. In a typical experiment the concentrate (4·17 g.), dissolved in a little benzene, was applied to the top of a column of silica gel (300 g.; 65 × 2·5 cm., activated at 200°/5 mm. for 1 hr.), and fractions were removed with benzene (i), 1 : 3 ether–benzene (ii), 3 : 1 ether–benzene (iii), and 1 : 9 methanol–ether (iv). Fraction (iii), rechromatographed (100 g.; 25 × 2·5 cm.), gave fractions with 1 : 3 ether–benzene (iii*a*), 3 : 1 ether–benzene (iii*b*), 1 : 9 methanol–ether (iii*c*), and 3 : 7 methanol–ether (iii*d*). Fractions iii*b* and *c* formed concentrate B (0·34% of the mixed acids). Further description of these fractions is summarised:

	Concentrate A	i	ii	iii	iv	iii*a*	iii*b*	iii*c*	iii*d*
Wt. (g.)	—	0·74	0·84	1·85	0·72	0·99	0·35	0·35	0·63
Glycol value (%)	55	0	24	64	94	48	74	76	—
$E^{1\%}_{1\,cm.}$ before isomern....	139	—	94	—	35	93	62	53	—
$E^{1\%}_{1\,cm.}$ after isomern. ...	473	—	247	—	121	368	489	482	—

Fraction iii*b* had $[\alpha]_D^{20}$ + 6·15° (2·6% ethanolic solution, 1 dm. tube). Despite the high glycol value of fraction iv this material differed from the other fractions in its behaviour on alkali-isomerisation and on hydrogenation and was not further investigated.

Preparation and Characterisation of (+)-15 : 16-*Dihydroxystearic Acid.*—Concentrate A (2·55 g.), at room temperature in the presence of 5% palladium–charcoal, took up 2 mols. of hydrogen. The product (2·43 g.), after a number of crystallisations from ethyl acetate and extractions with light petroleum (b. p. 60—80°), gave (+)-15 : 16-*dihydroxystearic acid* (1·02 g., 42%), m. p. 96—97°, $[\alpha]_D^{20}$ +3·3° (in 4% ethanolic solution; 2 dm. tube) (Found: C, 68·1; H, 11·6%; equiv., 320, 319, 312. $C_{18}H_{36}O_4$ requires C, 68·3; H, 11·5%; equiv., 316). The acid was converted by the Fischer–Speier procedure into the *methyl*, m. p. 89·5—90·5° (Found: C, 69·0; H, 11·5. $C_{19}H_{38}O_4$ requires C, 69·1; H, 11·6%), and *ethyl ester*, m. p. 74—74·5° (Found: C, 69·5; H, 11·5. $C_{20}H_{40}O_4$ requires C, 69·7; H, 11·7%).

A portion of concentrate B (130 mg.), similarly hydrogenated, gave the same product (75 mg.), m. p. 92—95° (58%; 77% based on the glycol value).

The glycol value (97% calc. as dihydroxystearic acid) of this acid (*ca.* 80 mg.) was determined and the oxidation fragments were recovered. The solution was diluted with water, and the white precipitate was treated in aqueous acetone with excess of permanganate solution. The resulting mixture was decolorised by sulphur dioxide and diluted, a solid separating (17 mg.), m. p. 96—109°. This m. p., raised to 107—111° by crystallisation from ethyl acetate and from nitromethane, was depressed (92—102°) with a crude but authentic sample of tridecanedioic acid (m. p. 105—114°) but remained unchanged (107—112°) with pentadecanedioic acid (m. p. 111—113°).

The solution remaining after removal of the above aldehydo-acid was steam-distilled (50 ml.) into 2 : 4-dinitrophenylhydrazine reagent. Next day this mixture which contained some orange precipitate was thoroughly extracted with chloroform, and the chloroform solution concentrated to 25 ml. and added to a 4 : 1 bentonite–kieselguhr column [17] (7·5 g.) which was then eluted with chloroform. An orange oil (15 mg.) was followed by a solid (45 mg.; m. p. 125—139°) which after several crystallisations from ethanol melted at 154—155° and was unchanged when mixed with a sample of propanal dinitrophenylhydrazone. The identity of these two was further proved by paper chromatography with two solvent systems.[18,19]

[17] Elvidge and Whalley, *Chem. and Ind.*, 1955, 589.
[18] Rice, Keller, and Kirchner, *Analyt. Chem.*, 1951, **23**, 194.
[19] Buyske, Owen, Wilder, and Hobbs, *ibid.*, 1956, **28**, 910.

Characterisation of (+)-*Dihydroxylinoleic Acid.*—The stock oxidising agent was a mixture of potassium periodate (22·43 g., 0·0975 mole) and potassium permanganate (0·395 g., 0·0025 mole) in 1 l. of aqueous solution which had to be warmed before use to effect complete dissolution of the periodate.

(a) *Oxidation of dihydroxylinoleic acid.* Concentrate B (78 mg.) was oxidised in an aqueous solution (300 ml.) containing *tert.*-butyl alcohol (90 ml.), the periodate–permanganate reagent (60 ml.), and enough potassium carbonate to give a pH of 8—9. The reaction was stopped after 8 hr. by addition of hydrochloric acid and enough sodium metabisulphite to convert all periodate, iodate, and iodine into iodide. The decolorised solution was basified, the butyl alcohol was distilled off under reduced pressure, and the remaining solution acidified and continuously extracted with ether. The extract was triturated with light petroleum (b. p. 40—60°): the soluble portion (7·1 mg.) was not identified, but the insoluble fraction (54 mg.) was azelaic acid (m. p. 100—104° after crystallisation from water, raised to 102—106° when mixed with an authentic sample).

(b) *Preparation of dihydroxylinoleyl alcohol.* A solution of the concentrate B (224 mg.) in anhydrous ether was added to lithium aluminium hydride (100 mg.) in the same solvent at such a rate that steady refluxing occurred. After 48 hr. at room temperature the mixture was decomposed with 4N-sulphuric acid and extracted with ether. The extract, when washed with carbonate solution and with water and evaporated, afforded the desired alcohol (195 mg., 91%).

(c) *Oxidation of dihydroxylinoleyl alcohol.* This alcohol (75 mg.), oxidised by permanganate–periodate, gave a crude product (51 mg.). The portion (36 mg.) insoluble in ice-cold light petroleum gave 9-hydroxynonanoic acid (15 mg., 35%), m. p. 40—46° (from ethyl acetate–light petroleum). This m. p. was raised to 46—49° (lit.,[20] 53°) and was then undepressed when mixed with an authentic sample. The *p*-bromophenacyl ester had m. p. 75—78°, slightly raised when mixed with an authentic sample.

(d) *Oxidation of oleyl alcohol.* A similar oxidation of oleyl alcohol (268 mg.) gave nonanoic acid (93%), characterised as its *p*-bromophenacyl ester, and 9-hydroxynonanoic acid [94%; m. p. 35—46°, raised to 45—51° (lit. 53°) when crystallised once from ether–light petroleum; *p*-bromophenacyl ester, m. p. 78—79°].

Infrared Studies.—(*a*) The spectrum of fraction iii*a* (48% diol) obtained with a Grubb-Parsons GS2A double-beam grating instrument showed no evidence of appreciable absorption in the 10·3 μ region.

(*b*) Olive, cameline, and vernonia oils were neutralised by passing a chloroform solution of each through a column of alumina. The corresponding mixed methyl esters were prepared by (i) acid hydrolysis with acetic acid, (ii) alkaline hydrolysis and recovery of the mixed acids, and (iii) esterification with anhydrous methanolic hydrogen chloride. Spectra in the region of 2·6—3·3 μ were measured for thin films of these oils and their esters.

Preparation of Tridecanedioic Acid.—Mixed acids (76 g.) of rape oil, crystallised from ethanol (200 ml.) and water (70 ml.) at 0°, gave a fraction of fairly pure erucic acid (9·3 g.; m. p. 31—34°, lit. 33°; I val. 73·3, theor. 75·0). This was oxidised by potassium permanganate–acetic acid,[19] and tridecanedioic acid separated from the aqueous solution after removal of the nonanoic acid. After one crystallisation from ethyl acetate (m. p. 106—111°, lit., 113°) it was considered pure enough for further reaction.

Preparation of Pentadecanedioic Acid.—Tridecanedioic acid (2·5 g.) was refluxed with pure thionyl chloride (10 ml.) for 2 hr., then volatile material was removed and the residual diacid chloride (2·85 g.) in pure ether (20 ml.) was added to excess of ethereal diazomethane. Next day the excess of diazomethane was distilled off with ether, and the solution concentrated to 20 ml. The bisdiazo-ketone (1·43 g.) which separated on cooling was dissolved in anhydrous methanol (20 ml.) in a conical flask fitted with a dropping funnel and connected to a gas-measuring burette. To this solution a 10% solution of silver benzoate in triethylamine (5 ml.) was added in 30 min. and the mixture was stirred for a further hour. During this time nitrogen evolution corresponded to 90% reaction. The solution was boiled and filtered, and the solvent removed from the filtrate. The residue, dissolved in a little ether and washed with a little alkali and water, gave crude dimethyl pentadecanedioate (2·16 g., 32% overall; m. p. *ca.* 40°, lit. 43°). This was hydrolysed by aqueous alcoholic potassium hydroxide; the crude acid (1·8 g.), purified

[20] Lycan and Adams, *J. Amer. Chem. Soc.*, 1929, **51**, 625.

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by crystallisation from ethyl acetate before and after vacuum-sublimation at 200°, had m. p. 111—113° (lit.,[21] 115°).

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[21] Chuit, *Helv. Chim. Acta*, 1926, **9**, 264.

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430. *An Additive Function of Entropy of Boiling, and the Prediction of Latent Heat of Vaporisation and Vapour Pressure of Liquids.*

By LEO H. THOMAS.

An additive function of entropy of vaporisation is presented by means of which latent heat and vapour-pressure data of a given substance can be evaluated from a knowledge of its b. p. only. The treatment also leads to a plausible correlation of molecular structure and internal order in the liquid state.

THE molar entropy of boiling, ΔS, of non-associated liquids at a given vapour pressure is approximately constant. The generalisation breaks down, however, for substances of high b. p., which have high values of ΔS, and for those of low b. p. and molecular weight, for which ΔS is very low. Attempts have been made to make ΔS more nearly constant by expressing it as a function of b. p.,[1] and Hildebrand [2] compared substances at temperatures corresponding to the same molecular concentration of vapour. The latter is generally assumed to be the more successful modification, but it is shown below that the two approaches are really equivalent, and therefore subject to the same limitations.

A theoretical examination of Hildebrand's and Trouton's rules requires the former to lead to more constant ΔS values.[3] There is no doubt that substances whose molecules permit of a degree of internal order in the liquid state tend to exhibit high ΔS values,[2] and a quantitative comparison of substances in terms of different degrees of internal order becomes possible if we choose a valid reference state characteristic of liquids of low internal order The difficulty lies in the fact that, owing to our inadequate knowledge of the liquid state, such a choice must be semi-empirical and arbitrary.

According to Pitzer,[4] the entropy of " perfect liquids " (heavier inert gases and methane; H_2, He, and to a lesser extent Ar, being excluded from quantum considerations) should be the same at corresponding states. This is indeed the case, and Pitzer and Guggenheim,[5] have shown that N_2, O_2, and CO conform fairly closely. For imperfect liquids, however, ΔS values differ greatly when compared at, say, the same reduced temperature, and increase rapidly with increasing liquid complexity.[6]

Imperfect liquids have been compared under the following conditions: (1) Staveley and Tupman [7] proceeded on the basis of Hildebrand's rule, and constructed a " reference entropy of vaporisation curve " from monatomic and " very symmetrical " molecules

[1] Partington, " An Advanced Treatise on Physical Chemistry," Vol. 2, Longmans, Green and Co., London, 1951.
[2] Hildebrand, *J. Amer. Chem. Soc.*, 1915, **37**, 970; *J. Chem. Phys.*, 1939, **7**, 233.
[3] Hirschfelder, Curtiss, and Bird, " Molecular Theory of Gases and Liquids," Wiley, New York, 1954.
[4] Pitzer, *J. Chem. Phys.*, 1939, **7**, 583.
[5] Pitzer and Guggenheim, *ibid.*, 1945, **13**, 253.
[6] See, *e.g.*, Pitzer, Lippmann, Curl, Huggins, and Petersen, *J. Amer. Chem. Soc.*, 1955, **77**, 3433 (Table 1).
[7] Staveley and Tupman, *J.*, 1950, 3597.

(Hg, Ar, Kr, Xe, CH_4, GeH_4, CMe_4, $SiMe_4$, and CCl_4), and ΔS values lying above the curve were interpreted in terms of different degrees of internal order or of restriction of molecular rotation. (2) Pitzer [4] concluded from theoretical considerations that comparison should be made at a constant ratio of vapour volume to liquid volume (a condition obeyed, of course, by the inert gases at corresponding states), and if this is correct, Hildebrand's rule is applicable only to substances of identical molar volumes in the liquid state.

Values of ΔS under these two different conditions for a number of substances are presented in Table 1, along with the values under "Trouton conditions." I calculated

TABLE 1.

Substance	ΔS (cal. mole^{-1} deg.$^{-1}$) V_g/V_l = 3125	$\log_{10} T/p$ (mm.) = 0·5	At v. p. = 100 mm.
CH_4		26·0	22·9
SiH_4		26·0	23·7
GeH_4		25·7	23·8
GeD_4		26·7 *	24·5
CMe_4		26·5	25·7
$SiMe_4$		26·5	25·9
$SnMe_4$		26·9	26·7
CCl_4	27·9	26·8	26·6
CF_4	27·3	28·2	25·6
$SiCl_4$		26·8	26·4
$GeCl_4$		26·2	26·0
$SnCl_4$		27·3	27·4
F_2	26·5	28·1	24·2
Cl_2	26·4	27·6	26·3
Br_2	27·1	27·9 *	27·4
I_2	27·1	27·2	27·8
C_6H_5F	28·6	27·6 *	27·4
C_6H_5Cl	28·7	27·2 *	27·4
C_6H_5Br	28·7	27·0 *	27·4
C_6H_5I	28·8	27·0 *	27·6
HCl	26·3	28·3	26·3
HBr	26·1	28·5 *	26·6
HI	27·2	28·4 *	27·1
CH_3F	27·0	28·6 *	26·7
CH_3Cl	26·9	27·7	26·5
CH_3Br	27·0	27·6	26·7
CH_3I	26·7	26·9 *	26·3

Substance	ΔS (cal. mole^{-1} deg.$^{-1}$) V_g/V_l = 3125	$\log_{10} T/p$ (mm.) = 0·5	At v. p. = 100 mm.
O_2 †		27·1	23·5
N_2 †		26·7	22·8
CO ‡		27·1	23·3
$CFCl{:}CF_2$		27·8 *	26·4
$CCl_2{:}CCl_2$		26·9 *	27·0
$CF_3{\cdot}CH_3$		28·4 *	26·9
$CF_2Cl{\cdot}CH_3$		27·9 *	26·9
$CCl_3{\cdot}CH_3$		26·9 *	26·6
$CHClF_2$		28·5 *	27·1
$CHCl_2F$		28·3 *	27·3
$CHCl_3$		27·7 *	27·3
$CH_3{\cdot}CHF_2$		28·7 *	27·4
$CH_3{\cdot}CHCl_2$		27·5 *	27·1
$CH_2{:}CF_2$		27·8 *	25·8
$CH_2{:}CCl_2$		27·1 *	26·5
$CF_2{:}CHCl$		27·8 *	26·7
$CCl_2{:}CHCl$		27·1 *	26·9
CF_3Cl		27·9 *	26·0
CF_2Cl_2		27·2 *	25·9
$CFCl_3$		27·1 *	26·4

* Values calculated from equation (4).
†‡ Vapour pressures from refs. 128 and 129 of Tables, respectively.

them by either of two methods, *viz.*, (1) first ascertaining, after the manner used by Pitzer and Hildebrand, the vapour pressure when V_g/V_l or $\log T/p$ has the required value, but then utilising my F and ΔS^r values (below) in order to arrive at more accurate corresponding values of ΔS than some previously reported; (2) from F and the b. p. as described on p. 2135. Such values have the advantage of being calculated under conditions such that (*a*) departure from ideal-gas behaviour on the part of the vapour can be ignored (corresponding vapour pressures for the Hildebrand procedure varying from 17 mm. Hg for N_2 to 125 mm. for I_2, and for the Pitzer procedure from 39 to 128 mm.), and (*b*) the three procedures can the more readily be compared. The following points are relevant:

(i) The tendency of ΔS to increase with b. p. is still apparent under Pitzer's conditions (highest values shown by halogeno-benzenes). (ii) Under Hildebrand's conditions, the ΔS values for the tabulated 15 fluoro-compounds are significantly higher (including the case of CF_4 of zero dipole moment) than the values for the corresponding chlorides by ~2% for each replacement of Cl by F. ΔS values for 9 bromine compounds (data for the

additional compounds tabulated in Tables 5 and 6 but not reproduced in Table 1 being used) on the other hand show no significant difference from the corresponding 9 chloro-compounds. Six iodo-compounds appear to give values ~1% lower per unit replacement than the ΔS for chlorine compounds, giving an order F : Cl : Br : I = 1·02 : 1·00 : 1·00 : 0·99. Under Trouton's conditions, the above order is reversed, giving F : Cl : Br : I = 0·99 : 1·00 : 1·01 : 1·02. Choice of Pitzer's basis of comparison leads to values of ΔS showing no significant difference from one halogen type to another. Any conclusions reached as to the extent of order in any of the above substances in the liquid state are likely, therefore, to be unreliable and may arise solely from an arbitrary basis for comparison. Hence it is conceivable that the high ΔS values of fluorine compounds when compared under Hildebrand's conditions could arise from their markedly higher volatility (by an " over-correction " for the dependence of ΔS on b. p.).

(iii) The fact that the tetrahydrides have lower ΔS values than those of the " globular " tetramethyl compounds is to be expected on the basis of their closer approximation to " perfect liquids." It is difficult, however, to account on this same basis for the fact that the tetrahalides (under Hildebrand's conditions) have still higher ΔS values—higher in fact than for such flexible and non-spherically-symmetrical substances as, *e.g.*: $CMe_3{\cdot}CH_2Me$, $\Delta S = 26{\cdot}3$; $CHMe_2{\cdot}CHMe_2$, $\Delta S = 26{\cdot}4$; $CMe_3{\cdot}CHMe_2$, $\Delta S = 26{\cdot}4$; $CHMe_2{\cdot}CMe_2{\cdot}CH_2Me$, $\Delta S = 26{\cdot}3$; $CH_2Me{\cdot}CMe_2{\cdot}CH_2{\cdot}CH_2Me$, $\Delta S = 26{\cdot}6$. It is difficult to believe that restriction of rotation in the spherically symmetrical molecules of the tetrahalides is greater than for such flexible hydrocarbons. Indeed, it appears [8] that rotation of the molecules of CCl_4 occurs, not only in the liquid state, but even in the solid state. Again, in the same way, the average of the ΔS values for O_2, N_2, and CO (27·0), believed by Pitzer and Guggenheim to approximate closely to perfect-liquid behaviour, should be compared with the values for, say, *n*-pentane (26·9) and *n*-hexane (27·1)—all figures calculated on the basis of Hildebrand's rule.

(iv) Comparison (again under Hildebrand's conditions) of data for carbonyl compounds with paraffins of the same chain length and degree of branching shows the latter to be uniformly lower, *e.g.*: $CH_2Me{\cdot}CH_2{\cdot}CHO$, $\Delta S = 27{\cdot}9$; $CHMe_2{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CHMe_2$, $\Delta S = 28{\cdot}1$; $CH_2Me{\cdot}CH_2Me$, $\Delta S = 26{\cdot}7$; $CHMe_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe_2$, $\Delta S = 27{\cdot}3$.

(v) As pointed out by Staveley and Tupman,[7] comparison under Pitzer's conditions likewise leads to surprising conclusions; *e.g.*, it was pointed out that ethyl acetate has a higher value of ΔS than water and ammonia in spite of the undoubtedly high degree of order arising from hydrogen-bond formation in the latter substances.

It is seen therefore that conclusions regarding relative order in liquids depend on the choice of comparison conditions and are not self-consistent, neither procedure used at present for imperfect liquids giving similar values of ΔS for substances having similar shape and therefore expected to exhibit similar degrees of molecular ordering.

In the absence then of an acceptable reference state, I attempted a new approach *via* structural contributions, in the hope that any departure from additivity could be interpreted in terms of degree and type of internal molecular order. As an empirical observation it immediately became apparent that, for substances incapable of rotational isomerism, the function $F = ZT/E$, where Z is the molecular number (sum of atomic numbers of constituent atoms) and $E/T = \boldsymbol{R}T\mathrm{d}\log_e p/\mathrm{d}T$ at a given vapour pressure p, is additive for the various atoms and bonds in the molecule. At sufficiently low vapour pressure (say at 100 mm. Hg or lower), F becomes ZT/L, where L is the molar heat of vaporisation. Such a treatment removes the difficulty of a choice of comparison conditions, and automatically allows, *e.g.*, of CF_4 possessing a different value of ΔS than CCl_4 without thereby carrying the assumption that the degree of order is different in the two substances. It is obvious therefore that the method, whilst possibly of limited applicability to the problem of order in liquids, seeks to interpret degree of ordering in a given substance over and above that which may appertain in the simplest molecules. The conclusions reached,

[8] Smyth, *J. Amer. Chem. Soc.*, 1939, **61**, 1695, 2798.

however, should be more acceptable than those arrived at on the basis of Hildebrand's or Pitzer's comparison conditions.

I have already shown [9] that the ratio of the values of E/T for any two non-associated liquids at temperatures corresponding to the same saturated vapour pressure is constant. The additive relationship is therefore generally valid no matter at what vapour pressure we choose to evaluate the additive constants. In this paper, all values are quoted for a vapour pressure of 100 mm. Hg.

It is readily seen that the treatment is equivalent to assuming that LZ_e/ZT is constant where Z_e ($\sim Z$) is the "effective molecular number," *i.e.*, $n_1k_1z_1 + n_2k_2z_2 + \ldots$, evaluated by summation of the contribution of n_1 atoms of an element of atomic number z_1, and so on. The numerical coefficients k_1, k_2, . . . are then characteristic of each element, and approximate to unity. It was hoped that these coefficients could be related to electron configuration and/or atomic polarisabilities, but all such attempts have failed, and it must be admitted that the additivity of F remains a purely empirical observation. It will be shown, however, that the function does lead to conclusions regarding order in the liquid state in keeping with the requirements of certain theoretical considerations.

Relationship between the Hildebrand and Trouton Entropies of Vaporisation and Boiling Point.—As pointed out by Hildebrand and Scott,[10] when $\log T/p$ is plotted against $\log p$ in order to ascertain the value of p at a given vapour concentration (*i.e.*, when $\log T/p$ has a chosen set value, c), a virtually linear plot is obtained. Furthermore, it becomes apparent that the plots are parallel, and differ only in the values of the intercepts they make with the $\log p$ axis. The value of $\log p$ corresponding to a given constant vapour concentration is therefore uniquely determined by the vapour pressure at any one temperature, *e.g.*, by the normal b. p. Hence we may write $(\log p_B - x)/(c + \log p_B - \log T_B) = K$, where x is the value of $\log p$ when $\log T/p = c$, and K is a universal constant. (The suffix B refers to normal boiling conditions.) With vapour pressure in mm. of Hg, and decadic logarithms, x becomes $(2{\cdot}881 - 3{\cdot}381K + K \log T_B)$ when conditions are chosen such that $\log T/p = \frac{1}{2}$. The "best" value of K was determined from the vapour pressures of 13 compounds of very diverse chemical nature and with b. p.s ranging from $-190°$ (N_2) to $+271°$ (*n*-pentadecane). The individual values did not show any dependence on b. p., and the average deviation from the mean, $K = 1{\cdot}094$, was 0·3%. We may therefore write

$$x = 1{\cdot}094 \log T_B - 0{\cdot}817 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Now it was shown previously [9] that the ratio of the value of ΔS for any given substance to the corresponding value ΔS^r for an "ideal reference substance" is constant independently of vapour pressure. Hence

$$(\Delta S)_{\text{Hildebrand}}/(\Delta S^r)_{\text{Hildebrand}} = (\Delta S)_{\text{Trouton}}/(\Delta S^r)_{\text{Trouton}}$$

The "Trouton conditions" being taken as a vapour pressure of 100 mm., which give $(\Delta S^r)_{\text{Trouton}} = 97{\cdot}4$, then

$$(\Delta S)_{\text{Hildebrand}} = 0{\cdot}01027(\Delta S^r)_{\text{Hildebrand}}(\Delta S)_{\text{Trouton}} \quad . \quad . \quad . \quad . \quad . \quad (2)$$

but, certainly [9] between the limits $p = 10$—1000 mm., ΔS^r is strictly a linear function of $\log p$; *i.e.*,

$$\Delta S^r = 141{\cdot}6 - 22{\cdot}1 \log p \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Combining equations (1), (2), and (3) we then get

$$\begin{aligned}(\Delta S)_{\text{Hildebrand}} &= (1{\cdot}640 - 0{\cdot}248 \log T_B)(\Delta S)_{\text{Trouton}} \\ &= Z(1{\cdot}640 - 0{\cdot}248 \log T_B)/F \quad . \quad . \quad . \quad . \quad . \quad (4)\end{aligned}$$

[9] Thomas, *J.*, 1953, 1233.
[10] Hildebrand and Scott, "Solubility of Non-electrolytes," 3rd edtn., Reinhold Publ. Corp., New York, 1950.

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which gives the relationship between (*a*) ΔS under the condition that $\log T/p = \frac{1}{2}$ and (*b*) ΔS at a vapour pressure of 100 mm.

Methods of Evaluation of F.—(1) The method generally preferred is by use of the equation

$$\log_{10}(T/100) = A + B\log_{10}(T/100)_{\text{benzene}}$$

benzene being used as reference substance in the manner indicated,[9] where $B = (T/E)(E/T)_{\text{benzene}}$, and solved by application of Campbell's "zero-sum" method[11] wherever possible. In some cases the vapour-pressure data are not sufficiently well spaced to allow of mathematical solution, and a graphical solution with a plot of log T against log T_{benzene} is more reliable. The value of $(E/T)_{\text{benzene}}$ at 100 mm. has been determined by numerical differentiation of the "best" vapour-pressure data[9] as 27·2 cal. mole^{-1} deg.$^{-1}$, so that $F = ZB/27{\cdot}2$. In this paper for convenience all such F values have been multiplied by 100.

(2) By differentiation of the three-constant Antoine equation $\log p_{\text{mm}} = \beta - [\alpha/(T - C)]$ in such cases where the constants have been accurately calculated, and from which F in the chosen units is given by $100/F = 4{\cdot}571\{\alpha(\beta - 2) + C(\beta - 2)^2\}/\alpha Z$. Values so calculated from the highly accurate data of the National Bureau of Standards are slightly but significantly higher than the corresponding values calculated by the first method by ~0·1% averaged over 70 compounds. It is not profitable to enquire whether such a small difference is due to a slightly inaccurate evaluation of $(E/T)_{\text{benzene}}$ by method (1), or due to failure of the Antoine equation to lead to correct values of d log p/dT. Indeed, it is surprising that any vapour-pressure equation containing only three constants should be so accurate. In order, however, to make values strictly comparable, all values calculated directly from the Antoine equation have been "corrected" by dividing by the factor 1·001. Differentiation of other three-constant equations such as, *e.g.*, the well-known Dupré–Kirchoff equation gives unreliable values of F.

(3) In certain cases, data are readily available only in the form of dT/dp (°C per 10 mm.) at the normal b. p. (in particular, Timmermans[12]) and from these the value of E/T at the b. p. can be readily calculated. The values corresponding to a vapour pressure of 100 mm. then follow by multiplying by a factor independent of the nature of the compound.[9] Hence $F = 3{,}040Z(\mathrm{d}T/\mathrm{d}p)/T_{\text{B}}$ where T_{B} is the b. p. (°K) at 760 mm. The method leads to values somewhat lower than those calculated by the first two methods for low-boiling liquids, and to values somewhat higher for high-boiling liquids. The difference varies approximately linearly with F from +0·5% for the lower paraffins to −1·5% for the C_{17}—C_{20} hydrocarbons. Again, for strict comparison, all values calculated by method (3) have been "corrected" by application of the equation

$$F_{\text{corr.}} = 1{\cdot}007F - 0{\cdot}000042F^2$$

(4) Data for many compounds have been published only in the form of the two-constant equation $\log p = \gamma - \delta/T$. Fairly reliable values of F can then be calculated from the equation $F/100 = Z(\log T_2 - \log T_1)/27{\cdot}2(\log T_2 - \log T_1)_{\text{benzene}}$, where T_2 and T_1 are the limits for which the equation is stated to hold, and $(T_2)_{\text{benzene}}$ and $(T_1)_{\text{benzene}}$ are the corresponding temperatures for benzene. Data published in the form of three- or more-constant equations, other than the Antoine equation, have been similarly used.

Comparison of the Methods.—Methods 2 and 3 ("corrected" as above) when applied to the same vapour-pressure data agree very closely. Thus for 70 hydrocarbons studied by the National Bureau of Standards, covering a normal boiling range of −161° to 343°, the average difference between the values calculated by the first two methods is 0·15%. Similarly the average difference for methods 2 and 3 is 0·2% for 64 hydrocarbons and over the same boiling range. The fourth method, tested on data published in the form of the

[11] Campbell, *Phil. Mag.*, 1920, **39**, 177; 1924, **47**, 816.

[12] Timmermans, "Physicochemical Constants of Pure Organic Compounds," Elsevier, Amsterdam, 1950.

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two-constant equation, gave results which did not differ systematically from those calculated by the other methods, the mean difference over 20 compounds of diverse types being 1·1%.

Reliability of F Values.—The absolute accuracy in the accurate measurements of the National Bureau of Standards is believed to be, on the average, about 0·2%, although reliability in individual cases might be a little less. Thus, method 2, applied to the data of Forziati, Norris, and Rossini,[13] and to the earlier data of Willingham, Taylor, Pignocco, and Rossini [14] for 15 hydrocarbons to which slightly different values for the Antoine constants were assigned at the two dates, leads to F values which agree to within 0·1%.

It is difficult to assess experimental error in the majority of other measurements. A rough idea may be gained by consideration of temperatures corresponding to vapour pressures of, say, 760 and 100 mm.; *e.g.*, for *n*-heptane, taking $T_{760} = 371{\cdot}5°$ and $T_{100} = 314{\cdot}9°$, we get $F = 212{\cdot}9$. An error in T_{100} of only 0·2° gives $F = 212{\cdot}0$, 0·4% lower than the previous figure (see also Table 7). It is believed that F values reliable to 1% necessitate very accurate determination of vapour pressure and elaborate purification of the materials. In the Tables, only mean F values are given in cases where more than one source of data has been employed, or when more than one method of evaluation has been applied to a given set of vapour-pressure values.

Additivity of F for Compounds Incapable of Rotational Isomerism. That F is additive for such compounds is evident from data in Table 5 using the series: (*a*) H_2 through HCl to Cl_2, (*b*) CH_4 by successive chlorination to CCl_4, (*c*) C_2H_4 through C_2H_3Cl, three isomers $C_2H_2Cl_2$, and C_2HCl_3 to C_2Cl_4, and (*d*) C_6H_6 through C_6H_5Cl to the three isomeric dichlorobenzenes. Graphical solution gives $F_{(Cl-H)} = 57{\cdot}3$.

Similar treatment for the series H_2 to Br_2, CH_4 to CBr_4, C_2H_4 to $CH_2{:}CHBr$, and C_6H_6 to $C_6H_4Br_2$ gives $F_{Br-H} = 120{\cdot}0$. Four intervals only are available for the corresponding cyanide series, *viz.*, H_2 to C_2N_2, CH_4 to $CH_3{\cdot}CN$, C_2H_4 to $CH_2{:}CHCN$, and C_6H_6 to $C_6H_5{\cdot}CN$, giving $F_{(CN-H)} = 38{\cdot}7$.

Calculation of the atomic and structural contributions (hereafter expressed as [H] etc.) now gives [2H] = 13, [CH_2] = 30, [Cl] = 64, [Br] = 127, [CN] = 45, [benzene] = 154, and [double bond] = 6. These values agree very closely with those ultimately evaluated (p. 2151) from more extensive data.

A stringent test for any additive function is to ascertain whether the value of [H] so determined agrees with the value for the element. (It is relevant that the value of the Trouton constant for hydrogen is less than half of the " normal " value.) Thus $F_{HCl} = 68{\cdot}4$ leads to [H] = 11; Cl_2 similarly to [15], HBr to [15], Br_2 to [15], HCN to [12], and C_2N_2 to [13], the mean value to the nearest significant figure being [13]. The figure derived from hydrogen itself is [13·3].

The Additivity Function for Paraffins.—Values of F for paraffins as well as for alkyl-*cyclo*pentanes and -*cyclo*hexanes, alkylbenzenes, and, except where otherwise indicated, for olefins, have been calculated by methods (2) and (3) from the data in " Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds," [15] supplemented and checked wherever possible by use of method (1) applied to the measured vapour pressures if published as such.[12,13,14,16] The values (by method 1) for the *n*-paraffins from methane to octane are those based on vapour pressures selected by Thodos.[17] As previously mentioned, the three methods agree so closely that the results are not tabulated since they may be so easily calculated from Antoine's equation.

From theoretical considerations it has been concluded [6] that " the decrease in entropy from the ideal gas state to some comparable state in the liquid region " would be greater

[13] Forziati, Norris, and Rossini, *J. Res. Nat. Bur. Stand.*, 1949, **43**, 555.
[14] Willingham, Taylor, Pignocco, and Rossini, *ibid.*, 1945, **35**, 219.
[15] American Petroleum Institute Research Project 44, Carnegie Press, 1953.
[16] Rossini *et al.*, *J. Res. Nat. Bur. Stand.*, 1950, **45**, 406; *J. Phys. Chem.*, 1956, **60**, 1446.
[17] Thodos, *Ind. Eng. Chem.*, 1950, **42**, 1514.

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for " globular " molecules than for molecules of simple fluids. Further, the behaviour of a non-polar substance of non-spherical shape is expected to conform closely to that of globular molecules.

I found, however, that under " Trouton conditions " the observed values of F for paraffins of chain length >3 carbon atoms are in good agreement with the values calculated on the basis of [C] = 17 and [H] = 6·5 derived as above; *i.e.*, the entropy of vaporisation of ethane, propane, *iso*butane, and *neo*pentane are all accountable on the basis of the same F increments. It seems likely therefore that any increase in ΔS expected for these compounds on the basis of departure from spherical shape as such is automatically allowed for by the choice of comparison conditions, or by the method of derivation of the structural parameters. It may be also that the effect is relatively small, undetectable within the limits of experimental accuracy in the determination of F. (Even in the case of *polar* non-flexible molecules, when the increase in ΔS over and above that of a simple fluid would be expected to be substantially higher, it is shown below that the effect is still qute small.) The extent of mutual alignment or of restricted " external " rotation of these substances is therefore held to be small or nil (but see allenes, p. 2144).

For normal paraffins C_nH_{2n+2}, where $n \geqslant 4$, and for their branched-chain derivatives, the values (F') calculated from the atomic constants are unquestionably higher than the experimental values by an amount (ΔF) clearly increasing with n. The physical interpretation of this appears to be that, in the liquid state, the longer molecules are arranged in an orderly manner with respect to neighbouring molecules, probably, from consideration of close-packing and their known configuration in the crystalline state, with the chain axes parallel.

Moore, Gibbs, and Eyring,[18] using Pauling's values for atomic dimensions and bond angles, compared the calculated molar volumes of *n*-paraffins with the experimental values on the basis of a regular zig-zag carbon chain (with the carbon atoms in one plane), and concluded that there are three liquid regions: at the lowest temperatures, the chains are interlocked, with the molecular spacings only slightly greater than their values in the crystalline solid; at higher temperatures, this condition gives way to a " libration " region where rocking of the molecules occurs, to be succeeded at still higher temperatures by a region of essentially free rotation of the molecules on their long axes, so that the liquid may now be visualised as a hexagonal close-packing of rotating cylindrical molecules. (Irrespective of which of these conditions may appertain at a given temperature for a given paraffin, the mere existence of parallel-packed zig-zag chains will add to the entropy of boiling, and the same remark would apply if the carbon atoms assumed a helical configuration as postulated by Mumford.[19]) In particular, it was concluded that at temperatures approaching (in the case of butane) or somewhat below the b. p. (with higher members), the *n*-paraffins higher than propane have attained such free rotation. Such a conclusion fits in well with the assignment of finite values to n commencing at unity for *n*-butane.

Methane as a sphere, and ethane as a cylinder of diameter 4·0 Å and length 5·5 Å, were held to be rotating even at their m.p.s. Propane, on the other hand, of corresponding dimensions 4·9 and 6·5 Å, was concluded to have incomplete rotation even at its b. p. With the possible exception of propane, therefore, the assignment of zero n value corresponds to the freely rotating cylinders of Moore *et al.*[18] However, my method leads to the further conclusion that in ethane and propane (and *iso*butane), the molecule as a whole has essentially free *external* rotation, and is not to be regarded as packing with its longer axis parallel to a neighbouring molecule. This conclusion seems likely from consideration of the above molecular dimensions, which show close approach to a spherical molecule with a ratio of longer to shorter dimensions of 1·37 for ethane and with a *lower* value 1·32 for propane. It seems, therefore, that the favoured configuration of, say, *n*-hexane can

[18] Moore, Gibbs, and Eyring, *J. Phys. Chem.*, 1953, **57**, 173.
[19] Mumford, *J.*, 1952, 4897.

be written with restricted rotation about the bonds printed in heavy type. Vaporisation then implies absorption of energy consumed in the " uncoiling " of the molecules. Rotation about the two end C–C bonds is free, since the terminal hydrogen atoms lie within the confines of the cylinder.

My treatment leads to the requirement that free rotation of methyl groups also occurs in (methyl) branched-chain derivatives, and indeed in methyl*cyclo*alkanes considered below; thus, *e.g.*, CH_3·CHMe·CHMe·CH_3 and CH_3·CHMe·CHMe·CHMe·CH_3 have to be assigned values of n of 1 and 2 respectively. How this arises in a close-packed assembly is difficult to see. (The above observations describe the average behaviour of the molecules, and it is not, of course, implied that no molecule ever suffers internal rotation about its C–C bonds. Rotation of a methyl group would presumably be statistically more probable on account of the smallness of the hydrogen atoms. Its moment of inertia is also low, and both factors may combine to give apparently free rotation.)

The above principles regarding the value of n apply in general to any chain of type A–B–C–D, where A, B, C, D are atoms other than hydrogen (but see special circumstances, below).

Values of ΔF plotted against n fall on a smooth curve passing through the origin, and up to $n \sim 8$, the plot is linear in agreement with the equation

$$\Delta S - (\Delta S)^1 = an; \text{ or } \Delta F = KnFF^1/Z \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

which implies that the difference in molar entropy between the experimental value and that value the substance would possess in the absence of the above-described molecular alignment is approximately proportional to the number of bonds about which rotation is thus restricted.

For values of $n > \sim 8$, eqn. (5) is only a first approximation, a more accurate fit being $\Delta S - (\Delta S)^1 = an - bn^2$. This implies that, under Trouton conditions, the longer chains are increasingly less ordered. It should be remembered that the corresponding temperatures are also increasing, which will operate against the tendency to mutual chain-alignment. The last equation is cumbrous; a closely related but more convenient one is

$$\Delta F = Z(k_1 n - k_2 n^2) = (\text{say})\ Z\Sigma \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where k_1 and k_2 are constants.

It is clear then that the " entropy of uncoiling " is

$$(L/T) - (L/T)^1 = (Z^2/FF^1)(k_1 n - k_2 n^2) \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Equation (6) was solved for the n-paraffin series from C_4H_{10} to $C_{20}H_{42}$, by use of [H] = 6·5 and [CH_2] = 30, to give $k_1 = 0{\cdot}0480$ and $k_2 = 0{\cdot}000622$.

A paraffin containing a *neo*-group is found to have a value of F significantly higher than the corresponding value for an isomer containing only *iso*-groups and of the same chain length. Examples will be found in Table 2. The percentage effect is small, and is considered to arise through interference with chain packing (closer approach to globular molecule behaviour). The behaviour of 30 such compounds in the paraffin and *cyclo*alkane series is in fact satisfactorily accounted for by assuming a reduction in n of 1/2 for each *neo*-group.

For two paraffins of the same chain length,

$$\Delta F_1 - \Delta F_2 = (Z_2 - Z_1)\Sigma \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

a quantity which is quite small and of value not materially affected by any final adjustment in the values of k_1 and k_2. A series (Table 2) derived from a given n-paraffin by successive replacement of hydrogen by methyl (other than at the terminal CH_3 groups) may then be visualised, and the values " corrected " by the use of (8) so as to be comparable with the

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F value for the *n*-paraffin. The *neo*-paraffins can be included by adjustment in the *n*-value.

TABLE 2.

Compounds	F	F adjusted for *neo*-group	Mean values	$Z-Z_{n\text{-}C_5H_{12}}$	$\Delta F-\Delta F_{n\text{-}C_5H_{12}}$	"Corrected" mean values	$[CH_3]-[CH_2]+[CH]$
$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3$	159·1	159·1	159·1			159·1	
$CH_3{\cdot}CHMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3$	189·0	189·0	188·8	8	0·8	189·6	30·5
$CH_3{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CH_3$	188·6	188·6					
$CH_3{\cdot}CHMe{\cdot}CHMe{\cdot}CH_2{\cdot}CH_3$ ...	217·4	217·4					29·6
$CH_3{\cdot}CHMe{\cdot}CH_2{\cdot}CHMe{\cdot}CH_3$ ...	217·0	217·0	217·7	16	1·5	219·2	
$CH_3{\cdot}CMe_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3$	218·9	217·6					
$CH_3{\cdot}CH_2{\cdot}CMe_2{\cdot}CH_2{\cdot}CH_3$	220·3	219·0					30·2
$CH_3{\cdot}CHMe{\cdot}CHMe{\cdot}CHMe{\cdot}CH_3$	246·3	246·3					
$CH_3{\cdot}CMe_2{\cdot}CHMe{\cdot}CH_2{\cdot}CH_3$	247·4	245·9	247·1	24	2·3	249·4	
$CH_3{\cdot}CMe_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_3$	249·5	248·0					
$CH_3{\cdot}CHMe{\cdot}CMe_2{\cdot}CH_2{\cdot}CH_3$	249·6	248·1					28·6
$CH_3{\cdot}CMe_2{\cdot}CHMe{\cdot}CHMe{\cdot}CH_3$ ...	276·8	275·1					
$CH_3{\cdot}CHMe{\cdot}CMe_2{\cdot}CHMe{\cdot}CH_3$ ...	277·0	275·3	275·0	32	3·0	278·0	
$CH_3{\cdot}CMe_2{\cdot}CH_2{\cdot}CMe_2{\cdot}CH_3$	279·3	275·8					
$CH_3{\cdot}CMe_2{\cdot}CMe_2{\cdot}CH_2{\cdot}CH_3$	277·3	273·8					31·8
$CH_3{\cdot}CMe_2{\cdot}CMe_2{\cdot}CHMe{\cdot}CH_3$ ...	311·4	307·5	306·0	40	3·8	309·8	
$CH_3{\cdot}CMe_2{\cdot}CHMe{\cdot}CMe_2{\cdot}CH_3$ ...	308·3	304·4					

We can in this way compile the following series from which the fundamental interval $[CH_3]-[CH_2]+[CH]$ may be evaluated by application of Campbell's method.[11]

Series	No. of CH_2 intervals	No. of compounds in series	Value of increment
C_3H_8 to CMe_4	2	3	30·5
n-C_4H_{10} to C_8H_{18}	4	6	29·6
n-C_5H_{12} to $C_{10}H_{22}$	5	17	29·9
n-C_6H_{14} to $C_{10}H_{22}$	4	20	30·0
n-C_7H_{16} to C_9H_{20}	2	13	29·8
n-C_8H_{18} to C_9H_{20}	1	4	30·2

In conjunction with 16 additional values similarly derived from alkyl-*cyclo*pentanes and -*cyclo*hexanes, and also from sulphides, thiols, and aliphatic nitro-compounds, the most probable value of the increment appears to be $29{\cdot}9 \pm 0{\cdot}2$.

For two isomeric paraffins differing by unity in chain length, we may write $\Delta F_2 - \Delta F_1 = Z(\Sigma_2 - \Sigma_1)$—a quantity again small and of value little affected by slight adjustment in the values of k_1 and k_2. A series of type

$$CH_3{\cdot}CHMe{\cdot}CH_2{\cdot}CH_3 \longrightarrow n\text{-pentane}$$

$$CH_3{\cdot}CHMe{\cdot}CHMe{\cdot}CH_3 \longrightarrow CH_3{\cdot}CHMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3, \text{ etc.}$$

can thus be built up, "correcting" for the difference in chain length as indicated.

A large number of such transitions occur in the paraffin series alone, and it was found that $[CH_3] + [CH] - 2[CH_2]$ is zero within the limits of experimental uncertainty. Hence $[CH_2] = 29{\cdot}9 \pm 0{\cdot}2$. The value of $[CH_3]$ derived from ethane and propane is 36·2, making $[CH] = 23{\cdot}6$ and $[C] = 17{\cdot}7$ (from CMe_4 and C_2Me_6). We thus have the values

	[C]		[CH]		[CH_2]		[CH_3]		F_{CH_4}
	17·7		23·6		29·9		36·2		43·6
Difference (= [H])		5·9		6·3		6·3		7·4	

leading to $[2H] = 13{\cdot}0$, a figure very close to the value 13·3 for hydrogen itself. Within the limits of accuracy, therefore, we may assume F[1] to be truly additive in the paraffin series, and write ("smoothing" the values for convenience): $[C] = 17{\cdot}0$, $[H] = 6{\cdot}5$, and $[CH_2] = 30{\cdot}0$, the same values as previously derived.

Final adjustment of the values of k_1 and k_2 was made by taking into account (*a*) the *n*-paraffin "equivalent" values derived as in Table 2 and subtracting 30·0 or a multiple of this figure from each F value, (*b*) the data for olefins, taking [double bond] = 5·5,

derived as below, and (*c*) the reliable data on sulphur compounds up to $n = 6$. The values finally selected were $k_1 = 0{\cdot}0480$ and $k_2 = 0{\cdot}000618$, which lie so close to those previously derived from the *n*-paraffin series alone that reassessment of the structural parameters was not necessary.

Those paraffins containing ethyl or higher-alkyl branches are given *n* values in accordance with a principle which is obvious from the examples

$CH_3{\cdot}CH_2{\cdot}CHEt{\cdot}CH_2{\cdot}CH_3$, $n = 3$. $F = 215{\cdot}2$; $F_{calc.} = 215{\cdot}0$
$CH_3{\cdot}CH_2{\cdot}CMeEt{\cdot}CH_2{\cdot}CH_3$, $n = 2{\cdot}5$. $F = 248{\cdot}2$; $F_{calc.} = 245{\cdot}3$.
$CHMe_2{\cdot}CH_2{\cdot}CHEt{\cdot}CH_2{\cdot}CH_3$, $n = 3$. $F = 270{\cdot}8$; $F_{calc.} = 269{\cdot}5$

The average deviation between experimental and calculated *F* values for 13 such compounds is 0·7%. Such an assignment of *n* values is further justified in connection with alkyl borates (p. 2150).

The average deviation for the 20 *n*-paraffins from methane to eicosane is 0·2%, for 27 *iso*-paraffins 0·3%, and for 24 paraffins containing *neo*- or *neo*- plus *iso*-groups 0·5%. In no case does the deviation exceed 1·0%. It is noteworthy that, for the higher *n*-paraffins, the fraction of the total entropy of boiling to be attributed to molecular uncoiling is substantial [*e.g.*, 16% for *n*-eicosane calculated from equation (7)].

TABLE 3. *Alkyl*cyclo*pentanes and alkyl*cyclo*hexanes.*

Compound	*F* (exptl.)	Methods used	*n*	ΔF (calc.)	$\frac{(F_{exptl.} - F_{calc.}) \times 100}{F_{calc.}}$	Ref.
*cyclo*Pentane	151·7	1, 2	0	0·0	+0·7	6, 8
cis-1 : 2-Dimethyl*cyclo*pentane	210·0	1	0	0·0	−0·3	16
trans-1 : 2-Dimethyl*cyclo*pentane	210·4	1	0	0·0	−0·1	16
1 : 1-Dimethyl*cyclo*pentane	211·3	1	0	0·0	+0·3	16
n-Propyl*cyclo*pentane	234·8	1, 2	2	6·0	±0·0	6, 16
n-Decyl*cyclo*pentane	402·5	2	9	45·9	−0·6	17
Perdeutero*cyclo*hexane	179·9	2	0	0·0	+1·3	18
1 : 1 : 3-Trimethyl*cyclo*hexane	272·8	1, 2	0	0·0	+0·8	6, 16
*iso*Propyl*cyclo*hexane	265·0	1	1	3·0	−1·0	16
n-Butyl*cyclo*hexane	289·0	1, 2	3	11·1	−0·2	6, 16
n-Decyl*cyclo*hexane	429·8	2	9	49·0	−0·4	17

References for Tables (independent of Text References).—(1) Keesom, Bijl, and van der Horst, *Proc. Acad. Sci. Amsterdam*, 1931, **34**, 1223. (2) Henning, *Z. Physik*, 1927, **40**, 775. (3) Giauque and Wiebe, *J. Amer. Chem. Soc.*, 1928, **50**, 101. (4) International Critical Tables. (5) Giauque and Powell, *J. Amer. Chem. Soc.*, 1939, **61**, 1970. (6) "Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds." (7) Thodos, *Ind. Eng. Chem.*, 1950, **42**, 1514. (8) Timmermans, "Physico-chemical Constants of Pure Organic Compounds," Elsevier, Amsterdam, 1950. (9) Zmaczynski, *J. Chim. phys.*, 1930, **27**, 503. (10) Dreisbach and Shrader, *Ind. Eng. Chem.*, 1949, **41**, 2879. (11) Young, *Sci. Proc. Roy. Dublin Soc.*, 1909—10, **12**, 374. (12) Barker, Brown, and Smith, *Discuss. Faraday Soc.*, 1953, **15**, 142. (13) Egan and Kemp, *J. Amer. Chem. Soc.*, 1937, **59**, 1265. (14) Kistiakowsky, Romeyn, Ruhoff, Smith, and Vaughan, *ibid.*, 1935, **57**, 876. (15) Castell-Evans, "Physico-chemical Tables," C. Griffin & Co., Ltd., 1902. (16) Forziati, Norris, and Rossini, *J. Res. Nat. Bur. Stand.*, 1949, **43**, 555. (17) Camin, Forziati, and Rossini, *J. Phys. Chem.*, 1954, **58**, 440. (18) Davis and Schiessler, *ibid.*, 1953, **57**, 966. (19) Ingold, Raisin, and Wilson, *J.*, 1936, 915. (20) Young and Fortey, *J.*, 1903, **83**, 45. (21) Willingham, Taylor, Pignocco, and Rossini, *J. Res. Nat. Bur. Stand.*, 1945, **35**, 219. (22) Forziati, Camin, and Rossini, *ibid.*, 1950, **45**, 406. (23) Ambrose, *Trans. Faraday Soc.*, 1956, **52**, 772. (24) Aston, Mastrangelo, and Moessen, *J. Amer. Chem. Soc.*, 1950, **72**, 5287. (25) Georgieff, Cave, and Blaikie, *ibid.*, 1954, **76**, 5494. (26) Powell and Giauque, *ibid.*, 1939, **61**, 2366. (27) Guttman and Pitzer, *ibid.*, 1945, **67**, 324. (28) Camin and Rossini, *J. Phys. Chem.*, 1956, **60**, 1446. (29) Cummings and McLaughlin, *J.*, 1955, 1391. (30) Rifkin, Kerr, and Johnston, *J. Amer. Chem. Soc.*, 1953, **75**, 785. (31) Dodd and Robinson, "Experimental Inorganic Chemistry," Elsevier Pub. Co., New York, 1954. (32) Burg and Wagner, *J. Amer. Chem. Soc.*, 1953, **75**, 3872. (33) Grau and Rath, *Z. anorg. Chem.*, 1930, **188**, 173. (34) Smits and Schoenmaker, *J.* 1924, **125**, 2554. (35) Berthoud, *Helv. Chim. Acta*, 1922, **5**, 513. (36) Brown and Robinson, *J.*, 1955, 3147. (37) Klemm and Henkel, *Z. anorg. Chem.*, 1932, **207**, 73. (38) Grisard, Bernhardt, and Oliver, *J. Amer. Chem. Soc.*, 1951, **73**, 5725. (39) Oliver and Grisard, *ibid.*, 1952, **74**, 2705. (40) King and Partington, *J.*, 1926, 925. (41) Kosolapoff, *J.*, 1955, 2964. (42) Schacherl, *Annalen*, 1880, **206**, 68. (43) Rintelin, Taylor, and Gross, *J. Amer. Chem. Soc.*, 1937, **59**, 1129. (44) Author's unpublished values. (45) Weissberger, Proskauer, Riddick, and Toops, "Organic Solvents," Interscience Pub. Inc., New York, 1955. (46) Li and Pitzer, *J. Amer. Chem. Soc.*, 1956, **78**, 1077. (47) Perry, "Chemical Engineers' Handbook," McGraw-Hill Book Co. Inc., New York, 1941. (48) Rex, *Z.*

phys. Chem., 1906, **55**, 355. (49) Stull, *Ind. Eng. Chem.*, 1947, **39**, 517. (50) Jik-Heng Hu, White, and Johnston, *J. Amer. Chem. Soc.*, 1953, **75**, 5642. (51) Mears, Stahl, Orfeo, Shair, Kells, Thompson, and McCann, *Ind. Eng. Chem.*, 1955, **47**, 1449. (52) Aston, Wills, and Zolki, *J. Amer. Chem. Soc.*, 1955, **77**, 3939. (53) Capps and Jackson, *J. Phys. Chem.*, 1956, **60**, 811. (54) Oliver, Grisard, and Cunningham, *J. Amer. Chem. Soc.*, 1951, **73**, 5719. (55) Whipple, *Ind. Eng. Chem.*, 1952, **44**, 1664. (56) Fowler, Hamilton, Kasper, Wieber, Burford, and Anderson, *ibid.*, 1947, **39**, 375. (57) Scott, McCullough, Good, Messerly, Pennington, Kincheloe, Hossenlopp, Jouslin, and Waddington, *J. Amer. Chem. Soc.*, 1956, **78**, 5457. (58) Smyth and Engel, *ibid.*, 1929, **51**, 2646. (59) Perry and Bardwell, *ibid.*, 1925, **47**, 2629. (60) Sinozaki, Hara, and Mitsukuri, *Bull. Chem. Soc. Japan*, 1926, **1**, 60. (61) Ruehrwein and Giauque, *J. Amer. Chem. Soc.*, 1939, **61**, 2626. (62) Heim, *Bull. Soc. chim. Belg.*, 1933, **42**, 461. (63) Douglas and Winkler, *Canad. J. Res.*, 1947, **25**, 281. (64) Klemenc and Wagner, *Z. anorg. Chem.*, 1938, **235**, 427. (65) Davis and Wiedeman, *Ind. Eng. Chem.*, 1945, **37**, 482. (66) Wise, *J. Amer. Chem. Soc.*, 1954, **76**, 3094. (67) Davies and Jenkin, *J.*, 1954, 2374. (68) McCullough, Scott, Pennington, Hossenlopp, and Waddington, *J. Amer. Chem. Soc.*, 1954, **76**, 4791. (69) Holcomb and Dorsey, *Ind. Eng. Chem.*, 1949, **41**, 2788. (70) Troops, *J. Phys. Chem.*, 1956, **60**, 304. (71) Gray and Pratt, *J.*, 1957, 2163. (72) Butler and Maass, *J. Amer. Chem. Soc.*, 1930, **52**, 2184. (73) Taylor and Layng, *J. Chem. Phys.*, 1933, **1**, 798. (74) Hubbard and Waddington, *Rec. Trav. chim.*, 1954, **73**, 910. (75) Scott, Finke, McCullough, Messerly, Pennington, Hossenlopp, and Waddington, *J. Amer. Chem. Soc.*, 1957, **79**, 1062. (76) Scott, McCullough, Hubbard, Messerly, Hossenlopp, Frow, and Waddington, *ibid.*, 1956, **78**, 5463. (77) Kennedy, Sagenkahn, and Aston, *ibid.*, 1941, **63**, 2267. (78) Nicolini, *Ann. Chim.*, 1951, **6**, 582. (79) Conner, Elving, and Steingiser, *Ind. Eng. Chem.*, 1948, **40**, 497. (80) Goodeve, *J.*, 1930, 2733. (81) Flom, Alpert, and Elving, *Ind. Eng. Chem.*, 1951, **43**, 1178. (82) Crenshaw, Cope, Finkelstein, and Rogan, *J. Amer. Chem. Soc.*, 1938, **60**, 2308. (83) Spence and Wild, *J.*, 1935, 506. (84) Smith and Bonner, *Ind. Eng. Chem.*, 1951, **43**, 1169. (85) Stross, Gable, and Rounds, *J. Amer. Chem. Soc.*, 1947, **69**, 1629. (86) Schumann, *Ann. Physik*, 1881, **12**, 40. (87) Rose, Acciarri, Johnson, and Sanders, *Ind. Eng. Chem.*, 1957, **49**, 104. (88) Wiberg and Sütterlin, *Z. anorg. Chem.*, 1931, **202**, 1. (89) Stock and Zeidler, *Ber.*, 1921, **54**, 531. (90) Copp, *Trans. Faraday Soc.*, 1955, **51**, 1056. (91) Thompson and Linnett, *ibid.*, 1936, **32**, 681. (92) Burg and Boone, *J. Amer. Chem. Soc.*, 1956, **78**, 1521. (93) Aylett, *J.*, 1957, 4152. (94) Fox, *J. Amer. Chem. Soc.*, 1950, **72**, 4147. (95) Jenkins and Chambers, *Ind. Eng. Chem.*, 1954, **46**, 2367. (96) Bradley, Mehrotra, and Wardlaw, *J.*, 1952, 5020. (97) Bullard and Haussman, *J. Phys. Chem.*, 1930, **34**, 743. (98) Charnley, Mortimer, and Skinner, *J.*, 1953, 1181. (99) Stone and Burg, *J. Amer. Chem. Soc.*, 1954, **76**, 386. (100) Zeltmann and Fitzgibbon, *ibid.*, p. 2021. (101) Dennis, Carey, and Moore, *ibid.*, 1924, **46**, 657. (102) Egloff, " Physical Constants of Hydrocarbons," Reinhold Pub. Corp., New York, 1946. (103) Mortimer and Murphy, *Ind. Eng. Chem.*, 1923, **15**, 11, 40. (104) Nelson and Senseman, *ibid.*, 1922, **14**, 58. (105) White, Barnard-Smith, and Fidler, *Ind. Eng. Chem.*, 1952, **44**, 1430. (106) Guthrie, Scott, Hubbard, Katz, McCullough, Gross, Williamson, and Waddington, *J. Amer. Chem. Soc.*, 1952, **74**, 4662. (107) Herrington and Martin, *Trans. Faraday Soc.*, 1953, **49**, 154. (108) Scott, Finke, Hubbard, McCullough, Gross, Williamson, Waddington, and Huffman, *J. Amer. Chem. Soc.*, 1950, **72**, 4664. (109) Guthrie, Scott, and Waddington, *ibid.*, 1952, **74**, 2795. (110) Heisig, *ibid.*, 1941, **63**, 1698. (111) Rathjens and Gwinn, *ibid.*, 1953, **75**, 5629. (112) Benson and Kistiakowsky, *ibid.*, 1942, **64**, 80. (113) Finke, Scott, Gross, Messerly, and Waddington, *ibid.*, 1956, **78**, 5469. (114) Stross, Monger, and Fink, *ibid.*, 1947, **69**, 1627. (115) Greenwood and Wade, *J.*, 1956, 1527. (116) Burg and Graber, *J. Amer. Chem. Soc.*, 1956, **78**, 1523. (117) Fenske, Myers, and Quiggle, *Ind. Eng. Chem.*, 1950, **42**, 649. (118) Hawkins and Armstrong, *J. Amer. Chem. Soc.*, 1954, **76**, 3756. (119) Kahlbaum, Stud. Dampfsp., II Abt., I Heft, 1897. (120) Kurbatow, *J. Russ. Phys. Chem. Soc.*, 1903, **35**, 319. (121) Clements, Wise, and Johnsen, *J. Amer. Chem. Soc.*, 1953, **75**, 1593. (122) Osborne and Ginnings, *J. Res. Nat. Bur. Stand.*, 1947, **39**, 453. (123) Scott and Brickwedde, *ibid.*, 1945, **35**, 501. (124) Pace and Aston, *J. Amer. Chem. Soc.*, 1948, **70**, 566. (125) " Arcton Refrigerants," Imperial Chemical Industries Ltd., 1957. (126) Hirschfelder, Curtiss, and Bird, " Molecular Theory of Gases and Liquids," Wiley, New York, 1945. (127) Tannenbaum, Kaye, and Lewenz, *J. Amer. Chem. Soc.*, 1953, **75**, 3753. (128) Kaye and Laby, " Physical and Chemical Constants," Longmans, Green & Co., London, 1944. (129) Crommelin, Byleveld, and Brown, *Proc. k. ned. Akad. Wetenschap*, 1931, **34**, 1314. (130) Simons and Dunlap, *J. Chem. Phys.*, 1950, **18**, 335.

*Alkyl*cyclo*pentanes and Alkyl*cyclo*hexanes* (see Table 3).—Methyl groups are again to be considered as free to rotate in the liquid state, and n is finite starting from an ethyl side chain as unity. The mean deviation is 0·35% over 36 compounds, taking [5 and 6 membered ring] = 0·7.

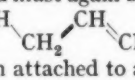
Alkylbenzenes.—The n values for *iso*propyl, *iso*butyl, *sec.*-butyl, and *tert.*-butyl, as well as for *n*-propyl- and higher *n*-alkyl-benzenes, are normal (Table 4). However, it is apparent that methyl groups are no longer " free " when attached to the benzene nucleus (see also pyridine homologues, Table 6). Thus each methyl group must be assigned a value of $n = 1$, the inference being that in the packing of such compounds in the liquid state, a time average fraction of the molecules possess rigid methyl groups. Whether this is due to hyperconjugation's stiffening the bond between the nucleus and the methyl group, or, which seems more likely, because the planarity of the molecule results in a particularly

close or stable packing, flat on flat, must remain undecided. It is relevant that a similar (but less pronounced) lowering of F is also apparent in the ethyl derivatives where hyperconjugation must be less important. Until additional data are available, each ethyl (or methoxy-group) is assigned an n value of 1·5. The alternative treatment of allotting an F increment as such to each CH_3 or ethyl group does not agree with the facts.

TABLE 4.

Compound	F exptl.	Methods used	n	$\Delta F_{calc.}$	Deviation (%)	Refs.
Hexadeuterobenzene	154·0	1, 2	0	0·0	+0·4	18, 19
1 : 2 : 3-Trimethylbenzene	236·2	1, 2	3	9·1	+0·1	6, 8, 16
1 : 2 : 4 : 5-Tetramethylbenzene	260·9	2	4	13·5	−0·2	6
Ethylbenzene	211·5	1, 2	1·5	4·1	+0·3	6, 20
2-Ethyl-*p*-xylene	264·4	2	3·5	11·8	+0·5	6
4-Ethyl-*o*-xylene	261·9	2	3·5	11·8	−0·5	6
1 : 2-Diethylbenzene	263·1	1, 2	3	10·2	−0·6	6, 16
*iso*Propylbenzene	239·2	1, 2	1	3·1	−1·1	6, 21
3-*iso*Propyltoluene	267·4	2	2	7·0	−0·2	6
2-*n*-Propyltoluene	264·0	2	3	10·2	−0·3	6
sec.-Butylbenzene	268·0	1, 2	2	7·0	±0·0	6, 16
n-Butylbenzene	264·4	1, 2	3	10·2	−0·2	6, 16
n-Decylbenzene	407·4	2	9	46·6	−0·2	17
Buta-1 : 2-diene	114·0	2, 3	1	1·4	+1·1	6
3-Methylbuta-1 : 2-diene	141·4	2	2	3·6	+0·6	6
Penta-2 : 3-diene	138·9	1, 2	2	3·6	−1·2	6, 22
Penta-1 : 2-diene	141·4	1, 2	1·5	2·7	−0·1	6, 22
Acetylene	52·6	2	0	0·0	+2·1	23
Methylacetylene	81	1, 3	0	0·0	−0·6	6, 8
Ethylacetylene	109·7	1	0	0·0	−1·6	24
Dimethylacetylene	111	1, 3	0	0·0	−0·4	6, 8
Vinylacetylene	104·5	1	0	0·0	+0·5	25
Propene	93·8	1, 2	1	1·1	−0·6	6, 26
But-1-ene	123·7	1, 2	1·5	2·2	+0·2	6, 8
Dodec-1-ene	329·3	1, 2	9	36·7	+0·2	6, 22
Eicos-1-ene	504·9	2, 3	17	102·0	+0·3	6
trans-But-2-ene	122·6	1, 2	2	3·0	+0·1	6, 27
2 : 3-Dimethylbut-2-ene	177·2	2, 3	4	8·7	+0·2	6, 28
cis-3-Hexene	178·5	2	3	6·6	−0·2	28
2-Methylpent-2-ene	177·5	2	3·5	7·7	−0·2	28
3 : 3-Dimethylbut-1-ene	183·1	2	0·5	1·1	−0·7	28
2 : 3-Dimethylbut-1-ene	181·5	3	2	4·5	+0·3	28
Buta-1 : 3-diene	114·8	2, 3	1	1·4	−1·6	6
2 : 3-Dimethylbuta-1 : 3-diene	172·9	2	3	6·1	+0·6	29
trans-Penta-1 : 3-diene	142·5	1, 2	2	3·6	−1·3	6, 22
Hexa-1 : 5-diene	174·1	2	3	6·1	+1·3	29
*cyclo*Pentene	143·2	1, 3	0	0·0	+0·1	6, 22
3-Methyl*cyclo*pentene	172·5	3	0	0·0	−0·3	6
1-Ethyl*cyclo*pentene	201·6	3	1·5	3·8	+1·1	6
1-Methyl*cyclo*hexene	201·0	3	1	2·5	+0·2	6

The F value assigned to benzene is 155·0. Now 6[CH] + [six membered ring] = 141·7. Hence the value of each " aromatic " double bond is 4·4, significantly lower than the value for a normal double bond. This lower value is considered to arise from the circumstance that the very flat (coplanarity of the carbon and hydrogen atoms) molecules of benzene are, at least partially, restricted to rotation in the plane of its own ring. Such a restriction is presumed absent from *cyclo*hexane and larger, saturated, ring compounds, and in the case of smaller rings, the molecules would not depart greatly from spherical shape. The normal double-bond value appears to appertain in the case of acyclic dienes.

Olefins and Dienes.—These are given expected n values; methyl groups attached to a carbon atom carrying a double bond must again be regarded as " rigid " (Table 4), *e.g.*, propene is to be regarded as packing  . Ethyl groups so attached also appear to be more restricted than when attached to a saturated carbon atom, and are allotted an

n value of 1·5. It is accepted for the remainder of the paper that n must increase by 1 or by 1·5 in all compounds having (*a*) a methyl or (*b*) an ethyl (or methoxy-) group, respectively, attached to any atom carrying a multiple bond, provided that rotational isomerism is possible about these groups (see ketones, esters, etc., below).

The mean deviation over 43 straight- and branched-chain olefins is 0·4%, over 11 alkyl*cyclo*pentenes and alkyl*cyclo*hexenes 0·7, and over 7 diolefins (conjugated and non-conjugated) 1·1.

Allenes.—Although data are to hand for only five compounds, it seems necessary to assign the value 3·6 to each double bond, the mean deviation being 0·7%. Two values of F for allene itself, calculated by methods (2) and (3) of ref. 6 to Tables, do not agree. The higher values of ΔS probably arise from the circumstance that allenes possess relatively long linear molecules giving rise to restricted (external) rotation.

Acetylenes.—Accurate data are available for only five compounds (Table 4). Owing to the linearity of the C–C≡CH group, n is taken as zero in ethylacetylene and also in methylacetylenes (compare cyanides, below). The mean deviation is 1·0%.

Deuterium Compounds.—The value of [D] appears to be slightly but significantly lower than that of [H]. By weighting the experimental values in proportion to the % of D in the compound, the most probable value is in accordance with [H] − [D] = 0·3, or, on the basis of [H] = 6·5, [D] = 6·2. F values for 7 deuterium compounds are included in the tables.

Halogen Compounds.—The substances so far considered have zero or small permanent dipole moments (μ), and the interaction potential arises essentially from London forces. The majority of compounds considered below, however, are polar, and it is of interest to ascertain whether it may be possible to correlate polarity with an increase in ΔS. Even in the favourable case of HCl (excluding compounds which are definitely associated, and where the hydrogen bonds result in a high degree of order), it has been calculated [20] that, in the gaseous state, dipole association forces make only a relatively small contribution (14%) to the van der Waals forces, and that the main contribution still arises from dispersion forces. Induced dipole association accounts for a still smaller contribution (2%).

In the gaseous state, when the distance apart of the molecules (r) is considerably greater than the length of the dipole, the energy of dipole interaction is given by $E_\mu = -\frac{2}{3}\mu^4/kTr^6$. Another limiting form, $E_\mu = -2\mu^2/r^3$, applies at very low temperatures.

In the liquid state, at close distance, the interaction not only depends on μ and r, but is also highly sensitive to the mutual orientation of the dipoles, being actually repulsive for a half of the possible solid angle. It is clear, then, that the magnitude of the contribution of dipole interaction to the energy and hence to ΔS in the liquid state is problematical, but is likely to be low compared with that arising from dispersion forces. It might also be that induced dipole interaction is now of greater relative importance, and this will depend on bond polarisabilities. In other words, knowledge of the mode and extent of molecular alignment is a pre-requisite to solution of the problem of total interaction in the liquid state. I believe that order due to dipole–dipole or dipole–induced dipole interaction will be superimposed on that arising from the considerations above, so that a chain including a polar group will be likely to be "stiffer," and mutual alignment statistically more probable, than in a non-polar hydrocarbon of the same length.

On such assumptions, F data for 9 chlorine compounds of zero μ give a weighted (according to estimated accuracy of the experimental data and the % chlorine in the compound) mean of [Cl] = 64·5 (see Table 5; Table 6 for $SiCl_4$, $SnCl_4$, and $GeCl_4$). On the other hand, a mean value of 63 (to nearest half unit) is derived from compounds with finite dipole moment (63·1 from 15 compounds of zero n, and 63·4 from 11 substances with flexible molecules). The increase in ΔS for polar chlorides is thus small, but believed to be significant.

[20] London, *Trans. Faraday Soc.*, 1937, **33**, 8.

TABLE 5.

Compound	F (exptl.)	Method of calcn.	Refs.	n	μ (D)	Deviation (%)
Hydrogen	13·3	1	1, 2, 126	0	—	+2·3
Deuterium	11·9	1	126	0	—	−3·4
Hydrogen deuteride	12·0	1	126	0	—	−5·8
Methane	43·6	1, 2, 3	6, 7	0	—	+1·4
Ethylene	64·4	2, 2, 3	6, 13, 14	0	—	−1·6
Benzene	154·5	—	—	0	—	−0·3
Chlorine	129·2	1	4, 5	0	Zero	+0·2
Carbon tetrachloride	278·6	1, 2	10, 11, 4, 12	0	,,	+1·3
p-Dichlorobenzene	266·8	1	10	0	,,	−1·6
trans-1 : 2-Dichloroethylene	179·7	1	8	0	,,	−1·0
Tetrachloroethylene	296·3	1	10	0	,,	−0·4
Hexachloroethane	427	1	8	1	,,	+2·7
Hydrogen chloride	68·4	1	3	0	1·0	−1·9
Methyl chloride	98·1	1	8	0	1·9	−0·4
Methylene chloride	155·9	1	8	0	1·6	−0·3
Chloroform	212·4	1, 3	4, 9	0	1·0	−1·5
Vinyl chloride	122·9	1	10	0	1·4	+1·0
1 : 1-Dichloroethylene	181·0	1	8	0	1·2	+0·6
cis-1 : 2- ,, ,,	177·1	1	8	0	1·9	−0·8
Trichloroethylene	237·9	1	4	0	0·9	−0·1
Chlorobenzene	211·7	1, 3	8, 15	0	1·7	+0·4
m-Dichlorobenzene	268·5	1	10	0	1·7	−0·1
o- ,, ,,	265·7	1	10	0	2·5	−0·8
1 : 1-Dichloroethane	184·5	2	46	0	2·1	−1·0
1 : 1 : 1-Trichloroethane	248	1	8	0	1·8	+1·3
Ethyl chloride	130·0	1	42	0	2·1	+1·3
*iso*Propyl chloride	158·7	1	8	0	2·2	+0·4
n-Propyl chloride	156	1, 4	4, 8, 49	1	2·0	−0·3
sec.-Butyl chloride	190·7	1	8	1	2·0	+2·5
Allyl chloride	149·4	1	45	1	2·0	+0·3
1 : 2-Dichloropropane	216·1	1	8	1	1·8	+1·0
1 : 2-Dichloroethane	182·7	1	49	1	1·2	−1·3
1 : 1 : 2-Trichloroethane	234·5	1	10	1	1·4	−3·2
1 : 1 : 2 : 2-Tetrachloroethane	302	1, 4	10, 4	1	1·4	+1·0
1 : 1 : 1 : 2-Tetrachloroethane	297·2	1	10	1	*2·0	−0·4
n-Butyl chloride	184·4	1	10	2	2·0	+0·4
n-Pentyl chloride	214·6	1	43, 44	3	2·0	+1·9
n-Hexyl chloride	234·3	1	44	4	2·1	−0·9
Fluorine	74·3	1	50	0	Zero	+0·4
Carbon tetrafluoride	164·0	1	8	0	,,	−0·6
Perfluoro*cyclo*butane	362·8	1	55	0	,,	−0·9
Perfluoroethane	252·4	4	124	1	,,	−0·2
Perfluoro-*n*-butane	431·6	1	56	3	,,	+2·2
,, *n*-pentane	497·0	4	130	4	,,	−1·4
,, *n*-heptane	667·6	1	56	6	,,	+0·9
Chlorotrifluoroethylene	211·7	2	54	0	0·4	−1·0
Chlorotrifluoromethane	192·3	1	49	0	0·4	+0·5
Chlorodifluoromethane	154·8	1	125	0	1·4	−1·9
Dichlorofluoromethane	182·8	1	125	0	1·3	−1·5
Fluorobenzene	182·7	2, 1	57, 15	0	1·6	+1·1
1 : 1 : 1-Trifluoroethane	156	1	8, 51	0	2·3	−1·0
Trichlorofluoromethane	250·2	1	8	0	0·4	+1·6
1 : 1-Difluoroethane	124	1, 4	51	0	*2·3	−2·5
1 : 1-Difluoroethylene	124	4, 1	51	0	1·4	+1·4
1-Chloro-1 : 1-difluoroethane	186	1, 4	51	0	2·2	+0·3
Methyl fluoride	67·5	1	8, 49	0	1·8	−0·9
Dichlorodifluoromethane	223·7	1	125	0	0·5	+2·3
1-Chloro-2 : 2-difluoroethylene	180·0	1	51	0	*1·0	−0·8
1 : 1-Dichlorotetrafluoroethane	304	4, 1	51	1	*1·0	−0·0
1 : 2- ,, ,, ,,	305·4	1	49	1	0·8	+0·2
Chloropentafluoroethane	281·0	1	52	1	0·8	+1·2
1 : 2 : 2-Trichlorotrifluoroethane	328·9	1	49	1	*1·5	−0·3
Perfluoromethyl*cyclo*hexane	622·0	1	56	1	*2·0	−0·3
3-Fluorotoluene	210·9	2	45	1	*1·6	+1·4
4- ,, ,,	211·1	2	45	1	1·8	+1·7
2 : 2 : 3-Trichloroheptafluorobutane	492·5	2	53	3	0·9	−1·3

* Estimated values.

TABLE 6.

Compound	*F* (exptl.)	Method of calc.	Refs.	*n*	Deviation (%)
Bromine	255·5	1	4	0	−0·2
Hydrogen bromide	135·3	1	47	0	+0·6
Methyl bromide	164·6	1	8	0	±0·0
Ethyl bromide	192·5	1, 3	48, 9	0	−0·8
n-Propyl bromide	225·3	4	4	1	+1·6
*iso*Propyl bromide	226·7	1	8	0	+1·0
Methylene bromide	281·5	1	49	0	−1·6
Tribromomethane	413·0	1	49	0	+1·2
Carbon tetrabromide	519·6	1	49	0	−2·1
Vinyl bromide	186·7	1	8	0	−0·2
1 : 2-Dibromoethane	311·1	1	10	1	−0·3
1 : 2-Dibromopropane	340·9	1	8	1	−0·2
Bromobenzene	277·1	3	9	0	+0·2
o-Dibromobenzene	395·7	1	10	0	−0·6
Iodine	381·7	1	15	0	−2·2
Methyl iodide	234·7	1	8	0	+1·4
Ethyl iodide	261·5	1	58	0	±0·0
*iso*Propyl iodide	296·0	1	8	0	+1·5
Iodobenzene	341·0	1	15	0	−0·7
Hydrogen iodide	199·3	1	49	0	−1·1
Cyanogen	89·4	1	47, 59	0	+1·6
Hydrogen cyanide	50·9	1	60, 61	0	+0·8
Methyl cyanide	80·6	1	10	0	+0·1
Ethyl cyanide	109·3	1	10, 62	0	−1·1
n-Propyl cyanide	137·2	1	8	1	−1·1
n-Butyl cyanide	165·2	1	10, 62	2	−0·6
n-Pentyl cyanide	192·0	1	10	3	−0·5
n-Hexyl cyanide	222·2	1	8	4	+1·3
n-Heptyl cyanide	244·2	1	8	5	−0·2
Cyanogen chloride	107·8	1	63, 64	0	+0·7
Cyanobenzene	192·8	1	8	0	+0·2
Vinyl cyanide	102·9	1	65	0	−0·1
Allyl cyanide	128·2	1	8	1	−2·4
cis-β-Methylvinyl cyanide	131·3	1	8	1	±0·0
trans-β-Methylvinyl cyanide	130·7	1	8	1	−0·3
cis-1-Cyanobuta-1 : 3-diene	149·5	2	66	1	−2·7
Chloropicrin	254·5	2	67	0	+1·2
Nitromethane	112·6	1, 2	10, 68	1	−0·4
Nitroethane	141·3	1	69	1·5	−0·3
1-Nitropropane	171·4	1	69	2	+0·8
2-Nitropropane	171·4	1	69	1	−0·5
1-Nitrobutane	196·5	1	69	3	−0·2
2-Nitrobutane	198·8	1	69	2	−0·2
2-Methyl-3-nitropropane	199·3	2	70	2	±0·0
Trimethylnitromethane	201·7	2	70	0·5	+0·7
2 : 2-Dinitropropane	240·6	1	69	1·5	−0·1
Ethyl nitrate	171·1	2	71	2	+2·4
n-Propyl nitrate	195·9	2	71	3	+1·1
*iso*Propyl nitrate	197·8	2	71	2	+0·8
n-Butyl nitrate	222·3	2	71	4	+1·1
*iso*Butyl nitrate	223·9	2	71	3	+0·5
Hydrogen sulphide	65·5	1	4	0	−3·8
Hydrogen disulphide	119·4	1	72	0	−3·0
Methanethiol	96·5	1	8	0	−1·5
Ethanethiol	126·6	1	8	0	−1·1
Propane-1-thiol	155·6	1	73	1	−0·3
Propane-2-thiol	156·2	2, 3	6, 74	0	−1·2
Butane-1-thiol	182·8	2, 3	6, 75	2	−0·3
Butane-2-thiol	185·7	3	6	1	±0·0
1 : 1-Dimethylethane-1-thiol	188·2	3	6	0	+1·4
Pentane-1-thiol	209·9	3	6	3	±0·0
Thiophenol	206·4	2	76	1	−0·4
Dimethyl ether	97·2	1	77	0	−2·9
Diethyl ether	153·7	3	8	2	−1·5
Methyl *n*-propyl ether	155·4	1	8	2	−0·4
Ethyl *n*-propyl ether	184·5	1	4	3	+0·8
Di-*n*-propyl ether	212·5	1	8	4	+1·4
Di*iso*propyl ether	213·1	2	78	2	−0·7

TABLE 6. (*Continued.*)

Compound	*F* (exptl.)	Method of calc.	Refs.	*n*	Deviation (%)
Di-*n*-butyl ether	262·0	1	10	6	+0·7
Di-*n*-pentyl ether	310·8	1	10	8	+0·5
Dimethyl formal	150·4	2	78	2	−1·7
Dimethyl acetal	181·8	2	78	2	−0·3
Diethyl formal	211·4	2	78	4	+2·3
Diethyl acetal	236·3	2	78	4	+0·5
Di-*n*-butyl acetal	333·3	1	79	8	±0·0
Chlorine monoxide	151·3	1	80	0	−1·2
Tetrahydrofuran	148·6	1	81	0	+0·7
Dioxan	170·4	1	82	0	−2·4
Formaldehyde	58·0	1	83	0	+0·9
Acetaldehyde	86·0	1	84	1	−0·5
Propionaldehyde	115·3	1	85	1·5	±0·0
n-Butyraldehyde	144·5	1	84	2	+0·5
Acetone	114·3	1, 3	8, 4	2	−0·2
Ethyl methyl ketone	142·7	1	10	2·5	−0·2
Diethyl ketone	170·7	1	10	3	−0·1
Di*iso*propyl ketone	230·9	1	10	2	−0·3
*iso*Butyl methyl ketone	200·0	1	43	3	−0·1
Di*iso*butyl ketone	280·0	2	85	4	−1·0
Methyl formate	112·2	1	8	1·5	+0·4
Methyl acetate	137·7	3	8	2·5	−1·2
Ethyl acetate	166·3	1, 3	8, 4	3	−0·7
Ethyl propionate	193·6	3	8	3·5	−0·7
Methyl *n*-butyrate	194·4	1	4	3·5	−0·3
*iso*Butyl formate	197·7	1	86	3	+0·7
*iso*Butyl acetate	223·3	1	86	4	+0·4
n-Butyl acetate	221·3	3	8	5	+0·8
Ethyl *n*-butyrate	222·2	1	86	4	±0·0
n-Propyl propionate	224·0	1	15	4·5	+1·3
n-Propyl *n*-butyrate	250·3	1	86	5	+1·0
Ethyl trimethylacetate	255·2	1	8	2·5	−0·2
*iso*Butyl propionate	249·2	1	86	4·5	−0·1
*iso*Propyl *iso*butyrate	253·8	1	8	3	−0·1
Methyl *n*-hexanoate	247·3	2	87	5·5	+0·4
*iso*Butyl *iso*butyrate	277·6	1	8	4	−0·6
Methyl *n*-octanoate	298·3	2	87	7·5	+1·0
Methyl borate	196·3	1	88	3	−0·8
Ethyl borate	275·4	1	88	6	+0·4
n-Propyl borate	345·3	1	43	9	−0·1
n-Butyl borate	416·9	1	43	12	+0·9
n-Pentyl borate	474·4	1	43	15	−0·6
Trimethylborine	123·5	1	89	0	−0·8
Triethylborine	207·1	1	4	3	−0·1
Dimethylmethoxyborine	148·7	1	32	1	−0·6
Dimethylfluoroborine	119·7	1	8	0	−3·8
Methoxydichloroborine	202·5	1	88	1	+0·3
Dimethoxychloroborine	202·3	1	89	2	+1·3
Ethoxydichloroborine	228·3	1	88	2	−0·1
Diethoxychloroborine	251·3	1	88	4	−0·2
Trimethylamine	128·8	1	8	0	−0·5
Diethylmethylamine	186·7	2	90	2	+1·0
Triethylamine	213·5	1	91	3	+0·9
NN-Dimethyl*cyclo*hexylamine	260·0	1	44	1	−1·4
Dimethylformamide	138·2	1	44	1	−2·8
Methyldimethylaminoborine	150·4	1	92	1	+0·9
Tetramethylhydrazine	184·7	1	93	1	−0·5
Phosphorus trichloride	246·0	1	15	0	±0·0
Phosphine	73·8	1	4	0	−3·6
Ethyldichlorophosphine	246·7	1	94	1	+0·1
n-Propyldichlorophosphine	270·6	1	94	2	−0·7
n-Butyl ,, ,,	295·0	1	94	3	−1·1
n-Pentyl ,, ,,	322·0	1	94	4	−0·3
n-Hexyl ,, ,,	353·3	1	94	5	+1·7
n-Heptyl ,, ,,	379·5	1	94	6	+2·1
Silane	76	1	4	0	−0·7
Disilane	139	1	4	0	−0·7
Methylsilane	107·3	1	4	0	+0·7

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TABLE 6. (*Continued.*)

Compound	*F* (exptl.)	Method of calc.	Refs.	*n*	Deviation (%)
Tetramethylsilane	193·3	1	8	0	−1·7
Tetrachlorosilane	310	1	49, 95	0	+0·5
Trichlorosilane	253·3	2	95	0	+2·9
Trimethylchlorosilane	221·0	2	95	0	−0·9
Methyltrichlorosilane	277·9	2	95	0	+0·7
Dimethyldichlorosilane	249·2	2	95	0	−0·1
Methylchlorosilane	160·9	1	4	0	−1·3
Methyldichlorosilane	221·9	1, 2	4, 95	0	+1·1
Ethyltrichlorosilane	299·0	2	95	1	−1·0
Diethyldichlorosilane	301·2	2	95	2	−0·2
1 : 2-Bistrichlorosilylethane	517·5	2	95	3	−0·3
Trichloro-1 : 2-dichloroethylsilane	404·6	2	95	2	−1·1
Phenyltrichlorosilane	378·9	2	95	1	−1·0
Vinyltrichlorosilane	303·7	2	95	1	+2·9
Ethylvinyldichlorosilane	295·7	2	95	2	+0·4
Triethoxyvinylsilane	358·1	2	95	7	±0·0
Triethoxyethylsilane	361·9	2	95	8	+0·2
Tetraethyl silicate	401·6	1	8	8	+3·8
Tetra*iso*propyl silicate	497·6	1	96	8	+0·7
Tin tetrachloride	431·0	1	15	0	−0·5
Tetramethylstannane	321·5	1	97	0	+0·2
Ethyltrimethylstannane	347·2	1	97	1	+0·2
Trimethyl-*n*-propylstannane	373·0	1	97	2	+0·4
Antimony trichloride	337·0	1	4	0	−0·0
Antimony tribromide	535·0	1	4	0	±0·0
Antimony tri-iodide	736·5	1	4	0	+0·1
Arsenic trichloride	305	4	4	0	−1·6
Trimethyl arsenite	303·3	1	98	3	+1·1
Dimethylarsine	203·0	1	99	0	+1·2
GeD_4	147	4	100	0	−0·8
Ge_2D_6	273	4	100	0	−3·9
Ge_2H_6	278	1	101	0	−2·5
Ge_3D_8	423	4	100	0	+0·9
Ge_3H_8	428	1	101	0	+1·6
GeH_4	151·4	1	49	0	+1·0
$GeCl_4$	383·8	1	49	0	+0·7
Naphthalene	244·0	1, 2	6, 102	0	−0·7
1-Methylnaphthalene	271·1	2	6	1	−0·4
2-Methylnaphthalene	271·4	2	6	1	−0·3
1-Ethylnaphthalene	294·2	2	6	1·5	−1·9
2-Ethylnaphthalene	295·4	2	6	1·5	−1·5
Phenanthrene	335·4	1	103, 104	0	−0·3
Anthracene	337·4	1	103, 104	0	+0·3
Indene	224·0	1	102	0	−0·1
Thiophen	160·7	2, 3	105, 6	0	+1·3
2-Methylthiophen	188·4	2, 3	105, 6	1	+1·0
3-Methylthiophen	188·1	2, 3	105, 6	1	+0·7
Furan	130·3	2	106	0	−0·2
Pyridine	150·1	1	107	0	−0·3
2-Methylpyridine	178·1	2	107	1	−0·1
3-Methylpyridine	178·2	2	107	1	−0·1
4-Methylpyridine	178·4	2	107	1	+0·1
2 : 5-Dimethylpyridine	205·7	2	107	2	+0·2
2 : 6-Dimethylpyridine	204·5	2	107	2	−0·3
Quinoline	238·0	1	15	0	−1·3
Nicotine	314·2	1	8	1	+1·1
*cyclo*Propane	93·3	1	8	0	+1·4
*spiro*Pentane	141·9	2	108	0	−1·6
Ethylene sulphide	117·8	2, 3	109, 6	0	+0·7
Ethylene oxide	87·2	2, 1	4, 8	0	−2·1
*cyclo*Butane	123·2	1, 2	110, 111	0	+1·0
*cyclo*Butene	115·6	1	110	0	+0·9
*cyclo*Butanone	135·5	1	112	0	−0·7
*cyclo*Heptane	208·5	2	113	0	+0·8
*cyclo*Hepta-1 : 3 : 5-triene	184·5	2	113	0	±0·0
*cyclo*Octane	236·9	2	113	0	±0·0
*cyclo*Octatetraene	204·0	1	8	0	−1·5
4-Methylpent-4-en-2-one	189·7	2	114	4	−0·3

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TABLE 6. (*Continued.*)

Compound	*F* (exptl.)	Method of calc.	Refs.	*n*	Deviation (%)
4-Methylpent-3-en-2-one	191·0	2	114	4	+0·4
α-Methylvinyl cyanide	131·0	2	45	1	−0·3
Acetyl chloride	143·1	1	115	1	+0·7
Methylbismethylthioborine	231·1	1	116	2	+1·1
Tetrahydronaphthalene	260·8	3	6	0	−0·7
cis-Decalin	291·0	1	117	0	+1·0
trans-Decalin	284·0	1	117	0	−1·5
*cyclo*Hexylbenzene	314·7	1	117	1	−1·2
Di*cyclo*hexyl	341·0	1	117	1	−0·8
*cyclo*Pentanone	166·4	1	112	0	+0·8
α-Pinene	280·2	1	118	1	−0·2
Nitrobenzene	225·0	1	8	1	−0·7
2-Nitrotoluene	250·2	1	10	2	+0·2
4-Nitrotoluene	251·2	1	10	2	+0·6
Benzaldehyde	195·4	1	8	1	−0·8
o-Chlorobenzaldehyde	257·0	1	10	1	+1·7
Benzoyl chloride	255·2	1	8	1	+1·0
Acetophenone	222·1	1	8	2	−0·6
p-Chloroacetophenone	279·1	1	10	2	+0·2
Propiophenone	244·5	1	10	2·5	−2·7
Benzophenone	323·0	1	10	2	−2·9
Dibenzyl ketone	369·5	1	15	4	−3·1
Methyl benzoate	248·8	1	10	2·5	+0·4
Phenethyl acetate	294·1	1	10	5	−0·4
Dimethylaniline	232·7	1	119, 120	1·5	−1·8
1-Chloro-4-ethylbenzene	263·6	1	10	1·5	−1·0
o-Methylstyrene	226·6	2	121	2	−2·1
m- ,,	228·8	2	121	2	−1·2
p- ,,	229·5	2	121	2	−0·9
o-Ethylstyrene	255·2	1	10	2·5	−1·5
m- ,,	250·4	1	10	2·5	−3·5
o-Chlorostyrene	264·5	1	10	1	+1·5
p- ,,	267·0	1	10	1	+2·4
o-Bromostyrene	334·7	1	10	1	+3·0
p- ,,	325·3	1	10	1	+0·1
Anisole	202·7	1	10	1·5	−2·5
Phenetole	227·8	1	10	2	−3·5
p-Chlorophenetole	280·9	1	10	2	−3·5
Phenyl *n*-propyl ether	262·7	1	10	3	+0·3
n-Butyl phenyl ether	288·0	1	10	4	+0·3

This further lowering in F due to dipole interaction being written as $(\Delta F)_\mu$, the corresponding increase in molar entropy of vaporisation, $(\Delta S)_\mu$, will be $\propto (\Delta F)_\mu/Z$. Making the simplest possible assumption (any more complicated function is clearly not justified at present) that $(\Delta S)_\mu$ varies directly with μ and inversely with the size (taken as $\propto Z$), we may write $(\Delta S)_\mu \propto \mu/Z \propto (\Delta F)_\mu/Z$, giving $(\Delta F)_\mu = c\mu$, where c is a constant. The average value of c is 1·3, and the deviation between the experimental values of F and those calculated on the basis of [Cl] = 64·5 and c = 1·3 is 1·0% averaged over all 32 chlorine compounds.

The value [F] = 37 was similarly derived from CF_4, F_2, and perfluoro*cyclo*butane, and also from the perfluoroparaffins C_2F_6, C_4F_{10}, and C_7F_{16}, μ of the last two compounds being assumed to be zero. The n values assigned to these two compounds are in agreement with the general principle outlined above, each terminal CF_3 group adding one unit to the chain length, and retaining the values of k_1 and k_2 derived essentially from hydrocarbon chains. The c value chosen was 3, thereby implying (as expected) that the dipole alignment in fluorides is of greater importance than in chlorides. In mixed chlorine–fluorine compounds, the higher c value associated with fluorides is assumed to apply. The mean deviation over 28 fluorine compounds is 1·1%.

Evaluation of c for polar substances other than fluorides and chlorides cannot be undertaken at present owing to paucity of data on suitable poly-derivatives of zero μ

(*e.g.*, in the bromine series, data are available only for bromine itself, the F value for CBr_4 being very unreliable). The atomic or structural constants for all other polar groups are therefore to be regarded as values which include any polar orientating effect. It may well be, on the other hand, that, apart from fluorine and chlorine compounds, the effect is too small to be detected; *e.g.*, in the hydrogen halide series, the effect would be expected to decrease in the order HCl>HBr>HI, in view of (*a*) the decrease in μ, and (*b*) the fact that the increasing size of the halogen atom from Cl to I prevents closeness of approach of neighbouring molecules and hence of significant mutual orientating effect.

It is to be understood, therefore, that all the compounds included in Table 6 have been treated on the assumption that the atomic or structural constants automatically include any dipole effect—including polyfunctional molecules which contain Cl or F (CCl_3CN, Cl_2O, $CH_3{\cdot}COCl$, etc.), and for which [Cl] = 63 and [F] = 36. The percentage deviation involved in this procedure will clearly be small except in the case of small molecules of either very low or very high polarity (the high negative deviations for, say, Me_2BF and $H{\cdot}CO{\cdot}NMe_2$ may arise in this way). The F values for symmetrical compounds possessing zero μ have, however, been calculated on the basis of [Cl] = 64·5 ($SiCl_4$, $SnCl_4$, $GeCl_4$).

Cyano-compounds.—The mean deviation is 1·1% over 17 compounds.

Nitro-compounds.—A mean deviation of 0·4% is shown by 9 nitro-alkanes; n must be such a value as to recognise extension of the chain by the terminal oxygen atom.

Alkyl Nitrates.—The mean deviation for 5 compounds is 1·2%, the same value of [NO_2] being used as in nitro-compounds, and [O] being taken as 27 as in ethers (see below).

Additivity Function for Compounds containing Bivalent Atoms or Radicals.—Sulphur compounds. The vapour pressures of a large number of sulphur compounds have been accurately measured by White, Barnard-Smith and Fidler,[21] and the corresponding F values have been calculated by using the published Antoine constants. Such values, for reasons already mentioned in connection with hydrocarbons, are not tabulated. Data for certain additional compounds have been taken from other sources (Table 6). As expected, the insertion of S into a carbon chain adds one unit to the total chain length, and for $-S-S-$ n is assumed to increase by 2. With [S] = 55, the deviation averaged over 15 alkyl sulphides is 0·4%, over 9 thiols 0·6%, and over 9 alkylthio*cyclo*alkanes 0·3%. The value of [S–S] (114) would appear to be higher, by 4 units, than 2[S], the mean deviation being 0·8% over 7 alkyl disulphides. The corresponding deviation, with [S–S] = 110, would be 1·8%.

Ethers. Sixteen oxygen compounds of diverse types are tabulated, the mean deviation being 1·1%.

Carbonyl compounds. The CO group, just like O or S, when inserted into a carbon chain, adds one unit to the total chain length. The mean deviation for 10 open-chain compounds is 0·4%.

Esters. The type $R{\cdot}CO{\cdot}OR$ has a chain length equal to that of $R{\cdot}CH_2{\cdot}CH_2R$. Methyl groups attached to the CO group (but not to the oxygen atom) are again to be regarded as " rigid " in the liquid state. It should be observed that the sum of the contributions [CO] + [O] = 71·5 is almost equal to the value [$-CO_2-$] = 71 assigned to esters. This small difference could obviously be due to uncertainty in the assessment of group contributions. The mean deviation is 0·6% over 17 compounds.

Additivity Function for Compounds containing Ter- and Quadri-valent Atoms.—The most extensive data are for boron compounds, the mean deviation being 0·8% over 13 compounds of quite diverse types. The value [N] = 20 should be considered provisional, being based on data for only 7 compounds. The value [P] = 57 is based in the main on the series $R{\cdot}PCl_2$. Vapour pressures were recorded in the literature only in graphical form, and the uncertainty in reading off individual values leads to some unreliability in the calculated F values. Table 6 also includes 21 silicon compounds, the mean deviation

[21] White, Barnard-Smith, and Fidler, *Ind. Eng. Chem.*, 1952, **44**, 1430.

being 1·1%, taking [Si] = 51, as well as 4 compounds of tin, 7 of germanium, and 3 each of antimony and arsenic.

Polynuclear aromatics and heterocyclics. Values calculated on the assumption that each (Kekulé) carbon–carbon double bond has the " aromatic " value 4·4 are in excellent agreement with the observed values. The value of [pyridine] is taken as 150·6.

Compounds containing three- and four-membered rings. Seven such compounds show a mean deviation of 1·2%, [3 and 4 membered rings] being taken as = 2.

Compounds containing seven- and eight-membered rings. Four such compounds show a mean deviation of 0·6% if we take [7 and 8 membered rings] = − 3. The double bonds in *cyclo*hepta-1 : 3 : 5-triene and in *cyclo*octatetraene are assumed to be of normal, *i.e.*, non-aromatic, type.

Compounds of Hybrid Type.—The last section of Table 6 lists 41 polyfunctional substances not taken into consideration in the earlier evaluation of atomic and structural constants. It includes many data of questionable reliability, and the mean deviation of 1·3% can be regarded as satisfactory. The somewhat large deviations shown by styrene derivatives (mean 1·8% over 9 compounds) might be expected on the grounds of possible polymerisation during measurements. Large negative errors are exhibited by propiophenone (2·7%), benzophenone (2·9%), anisole (2·5%), and phenetole (3·5%). All four measurements were carefully carried out on materials estimated as of 99·6—100 mole % purity, and it would appear that such errors lie outside the limits of experimental error.

Compounds containing Elements in Higher Valency States.—The observed values of F for such compounds are consistently lower by appreciable amounts than the values calculated on the basis of the atomic constants previously evaluated. Structural increments in respect of possible double bonds would still further increase the discrepancy. Owing to insufficient data, the behaviour cannot yet be rationalised, and a few examples will suffice (Table 7).

TABLE 7.

Compound	F (exptl.)	F (calc.)	Diff. (%)	Refs.	Method of calcn.	Compound	F (exptl.)	F (calc.)	Diff. (%)	Refs.	Method of calcn.
B_2H_6	63·5	69·0	9	30	1	SF_6	220·0	271·0	23	37	1
B_5H_{11}	130·3	146·5	12	31	1	ClF_3	149·3	171·0	15	38	2
$Me{\cdot}PH_2{,}BH_3$	121·0	141·0	17	32	1	BrF_3	199·8	236·0	18	39	2
SO_3	103·0	136·0	32	33, 34, 35	1	ClO_2	109·3	117·0	7	40	1
						$Me{\cdot}PO(OMe)_2$	214·2	241·3*	13	41	1
SF_4	174·9	199·0	14	36	1						

* Taking $n = 2$.

Associated Compounds.—Alcohols, phenols, primary and secondary amines, and amides have F values considerably lower than the values calculated on the basis of monomeric formulæ, owing to the absorption of energy in the breaking up of the polymers. I hope in

List of atomic and structural constants.

H	= 6·5	Zn	= 120	C–C treble bond	= 4·5
D	= 6·2	Ge	= 123	3- & 4-membered rings	= 2
B	= 15	As	= 121	5- & 6- " "	= 0·7
C	= 17·0	Se	= 121	7- & 8- " "	= −3
N (tertiary)	= 20	Br	= 128	−C≡N	= 44
O	= 27	Sn	= 175	−CO−	= 44·5
F	= 36 (37)	Sb	= 148	−CO−O−	= 71
Si	= 50·5	I	= 195	$-NO_2$ (nitro)	= 78
P	= 57	C–C double bond	= 5·5	Pyridine	= 150·6
S	= 55	C–C double bond (aromatic)	= 4·4	Benzene	= 155·0
Cl	= 63 (64·5)	C–C double bond (allene type)	= 3·6		

the immediate future to re-examine my views on molecular association [22] in the light of the more accurate estimates of entropies of boiling now presented.

Estimation of Latent Heat and Vapour Pressure of Liquids.—If vapour-pressure data are

[22] Thomas, *J.*, 1948, 1345, 1349.

to hand, the latent heat of vaporisation of a given compound at any temperature up to the critical can readily and conveniently be calculated in the manner described earlier.[23] The present paper supplements these methods in the case of a compound whose b. p. is known at one pressure only. Thus the b. p. (T°K) under any other pressure can be evaluated from the equation

$$\log_{10} T = \log_{10} \theta + (F/Z)(Z/F)_{\text{benzene}} \log_{10} (T/\theta)_{\text{benzene}}$$

where T_{benzene} and θ_{benzene} are the b. p.s of benzene under the same two pressures, and F is the value calculated from the atomic and structural constants and equation (6). This equation can obviously be used to calculate θ_{benzene} from a known T value. The vapour pressure of benzene at θ_{benzene} then, of course, equals that of the substance at T°. Table 8 shows the b. p.s of a number of hydrocarbons under a pressure of 10 mm. so calculated from the b.p.s under 760 mm. Hg. The magnitude of the error likely to be involved in this procedure has been discussed on p. 2136. In Table 8 the average deviation involved in the calculation of T is 0·2°, whereas the mean deviation in the corresponding calculated F values is 0·4%.

TABLE 8.

$\log_{10} (T/100) = \log_{10} (\theta/100) - 0{\cdot}03742F/Z.$

Substance	B. p. (°c)/10 mm. Exptl.	Calc.
Ethane	−142·9	−143·0
Propene	−112·1	−112·5
Penta-1 : 4-diene	−57·1	−57·5
n-Pentane	−50·1	−50·0
*cyclo*Pentane	−40·4	−40·0
3-Methylpentane	−30·1	−29·9
2 : 3-Dimethylpentane	−10·3	−10·3
Methyl*cyclo*hexane	−3·2	−3·2
cis-1-Ethyl-2-methyl*cyclo*pentane	14·5	14·3
Ethylbenzene	25·9	26·1
2 : 3 : 3 : 4-Tetramethylpentane	27·2	26·9
Non-1-ene	35·5	35·9
1 : 4-Diethylbenzene	62·8	62·6
n-Butylbenzene	62·4	62·6
n-Dodecane	91·6	91·3
Hexadec-1-ene	147·3	147·5

To find the latent heat of vaporisation (Table 9) at a temperature T°(K), it is first necessary to calculate from the known b. p. the corresponding vapour pressure as above. The value of E then follows from the relationship $E = ZTx/F$, where x is the ratio of the value of E/T at the determined vapour pressure to its value at 100 mm. pressure. The method to be used in evaluating x has been outlined in ref. 9, Table 1.

TABLE 9.

Substance	T (°K)	p (mm.) (calc.)	p (mm.) (exptl.)	l (cal./g.) (calc.)	l (cal./g.) (exptl.)	Refs.
n-Octane	298·1	14·2	14·0	86·3	86·8	122
3-Methylheptane	,,	19·8	19·5	82·9	83·3	,,
2 : 5-Dimethylhexane	,,	30·7	30·4	78·9	79·2	,,
2 : 2 : 5-Trimethylhexane	,,	16·7	16·6	74·3	74·9	,,
Toluene	,,	28·2	28·4	99·8	98·6	,,
Ethylbenzene	293·9	7·3	6·8	95·7	95·6	123

At temperatures sufficiently removed from the b. p. (say, below ~50 mm., when the difference between E and L will not exceed ~½%), we may equate E to L, so that the latent heat per g. $= ZTx/MF$. Its value at any temperature up to the critical may then be calculated in the manner previously outlined.[23]

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[23] Thomas, *J.*, 1949, 3415.

431. *Michael Additions to Methoxy-*p*-benzoquinone.*

By J. A. D. Jeffreys.

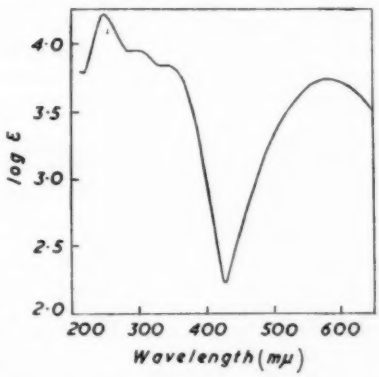
Methoxy-*p*-benzoquinone undergoes Michael additions to give compounds of type (I; R, R′ = CO_2Alk, CN, Ac); displacement of the methoxyl group can also occur. The products readily cyclise, giving a lactone or a furan. In alkaline solution, compounds of type (I) are readily oxidised by air to the blue anion of the corresponding quinone.

Methoxy-*p*-benzoquinone was prepared from methoxyquinol by use of dichromate [1a] in weakly acid solution.[1b] Michael additions of diethyl and dimethyl malonate, ethyl cyanoacetate, malonodinitrile, and ethyl acetoacetate to this quinone were made with an alkoxide ion as catalyst (method 1). In addition, diethyl malonate and ethyl cyanoacetate were added with ammonia as catalyst (method 2). Primary products of type (I; R and R′ = CO_2Alk, CN, or Ac) were isolated, except that the product from ethyl acetoacetate was unstable. These dissolved in weak alkali (*e.g.*, sodium hydrogen carbonate solution) with the production of an intense blue colour, which was stable for several hours but was rapidly destroyed in 2N-sodium hydroxide.

Table 1. *Absorption maxima (mμ; approx.) in the visible spectrum of the anions of some Michael addition products derived from* p-*benzoquinone.*

Product from	$\lambda_{max.}$ [a]	Product from	$\lambda_{max.}$
p-*Benzoquinone and:*		*Methoxy-*p*-benzoquinone and:*	
Et_2 malonate	585	Et benzoylacetate	540
*Methoxy-*p*-benzoquinones and:*		Acetylacetone	530 [b]
Et_2 malonate	585	Dimedone	530 [c]
Et cyanoacetate	605	Nitromethane	580 [d]
Malonodinitrile	605	(Quinone alone)	None [e]
Et acetoacetate	530		

[a] Solutions blue. [b] Solution blue, rapidly becoming purple. [c] Very weak; solution purple. [d] Very weak; solution pink. [e] Solution green, becoming brown.



Absorption spectrum of the anion of 5-(*diethoxycarbonylmethyl*)-2-*methoxybenzo*-1:4-*quinone in* N/1000-NaOH *containing* 8% *by volume of* 95% *ethanol.*

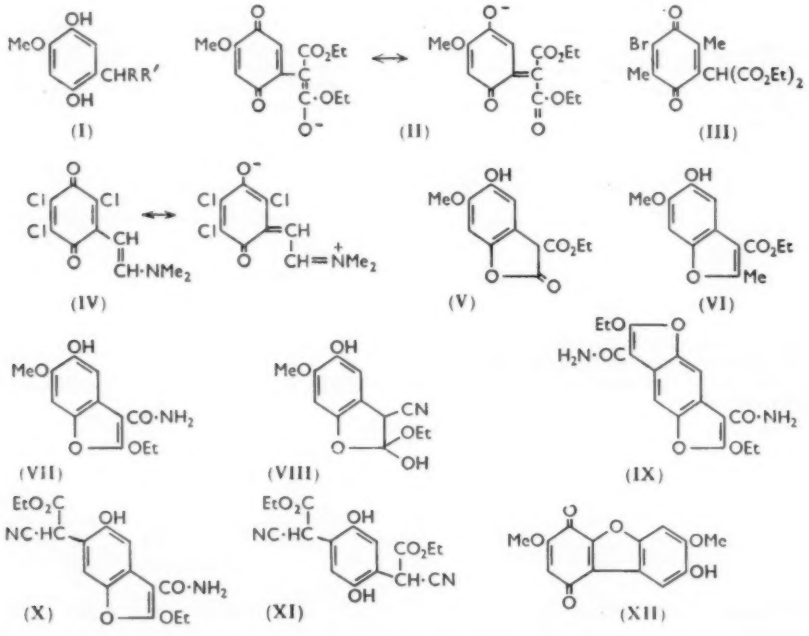
Oxidation of the adduct (I; R = R′ = CO_2Et) with acidified dichromate gave the corresponding quinone as an oil. Like the parent quinol, this dissolved in alkali to a deep blue solution which, after acidification, showed ultraviolet absorption maxima at the same wavelengths as a solution of the pure quinone, but with ε values decreased by about 10%. Thus, the blue colour is that of the anion of the quinone (II); the two chief canonical structures of the resonance hybrid are shown. That similar quinones form stable anions

[1] (*a*) Dimroth, Eber, and Wehr, *Annalen*, 1926, **446**, 147; (*b*) Erdtmann, *Proc. Roy. Soc.*, 1934, *A*, **143**, 191.

has long been known, and it has been stated [2] that the quinone (III) is a stronger acid then diethyl malonate. Attempts to prepare quinones from the quinols (I; R = CO_2Et or CN, R′ = CN) failed, but solutions of these quinols in N/1000-sodium hydroxide, of such a concentration that the dissolved oxygen would be enough for complete oxidation to the quinones, had absorption spectra that were qualitatively very similar to that of the anion (II) (Figure), compound (I; R = CO_2Et, R′ = CN) having $\lambda_{max.}$ 236, 302, 350, and 605 mμ, and (I; R = R′ = CN) 242, 300, 363, and 605 (inflection at 490) mμ. Table 1 shows the dependence of the position of maximum absorption in the visible spectrum on the nature of the methylene component. Dialkylaminovinylquinones [3] (*e.g.*, IV), the structure of whose resonance hybrid resembles that of the anion (II), show light absorption similar to that of this anion.

TABLE 2. *Infrared bands (cm.$^{-1}$) between* 1650 *and* 2500 *cm.$^{-1}$* (recorded by a Grubb–Parsons Type 54 instrument, with the samples in KCl discs).

Compound	Band	Assignment
(I; R = R′ = CO_2Et) ...	1739	CO (Ester)
(V)	1739	CO (Ester)
	1815	CO (Lactone)
(I; R = CO_2Et, R′ = CN	1736	CO (Ester)
	2273	CN
(VII)	1667 (infl.)	CO (Amide)
(IX)	1672	CO (Amide)
	2358	Not known
(X)	1675	CO (Amide)
	1745	CO (Ester)
	2273	CN
	2353	Not known
2 : 5 : 1 : 4-$(HO)_2C_6H_2(CH_2{\cdot}CO_2Et)$	1715	CO (Ester)
	2310	Not known
	2420	



On treatment with acid, the primary adducts readily underwent ring-closure; the quinol (I; R = R′ = CO_2Et) gave the lactone (V), and the chief crystalline product isolated from the reaction of methoxy-*p*-benzoquinone with ethyl acetoacetate was the benzofuran (VI). The quinol (I; R = CO_2Et, R′ = CN) gave an isomer formulated as

[2] Smith, Arnold, and Nichols, *J. Amer. Chem. Soc.*, 1943, **65**, 2131.
[3] Buckley, Henbest, and Slade, *J.*, 1957, 4891.

(VII), since the compound has no ester-carbonyl or nitrile band in the infrared spectrum (the parent quinol has both bands), nor has it a lactone-carbonyl band; however, it has a band at 1667 cm.$^{-1}$, suggesting an amide group. If structure (VII) is correct, it is possible that it is formed by rearrangement of the ortho-ester (VIII).

When made by method (1), the quinol (I; R = CO_2Et, R′ = CN) was accompanied by several other compounds. Analyses of two of these indicated formula $C_{16}H_{16}O_6N_2$, and on the basis of their infrared spectra (see Table 2) these compounds are formulated as (IX) and (X). The former appears to be the same as the adduct from *p*-benzoquinone and ethyl cyanoacetate described by Wood *et al.*[4] as the quinol (XI). Acid hydrolysis of compound (IX) and then esterification gave 2 : 5-di(ethoxycarbonylmethyl)quinol, identical with a sample prepared by the method of Wood *et al.* Displacement of a methoxyl group by the anion of the methylene component was not noticed in any of the other cases; nucleophilic displacements of a similar type have, however, been described before.[3,5]

Although the quinols of type (I) were readily oxidised by air in weakly alkaline solution to the anions of the corresponding quinones, treatment of the quinol (I; R = CO_2Et, R′ = CN) with acidified dichromate gave no simple quinone, but a very small yield of a red substance whose ultraviolet absorption resembles that of the dibenzofuran (XII) produced by acid-catalysed or thermal rearrangement of 4 : 4′-dimethoxydiphenyl-2 : 5 : 2′ : 5′-diquinone.[6]

Experimental

Ultraviolet spectra were measured on a Unicam S.P. 500 spectrophotometer. Woelm acid alumina was used throughout, and the dry powder measured by volume; Roman numerals refer to the Brockmann grade, prepared according to the makers' instructions; before use, the alumina was exposed to sulphur dioxide. Unless otherwise stated, light petroleum had b. p. 40—60°.

*Methoxy-*p*-benzoquinone.*—Methoxyquinol was prepared from vanillin by a method prescribed[7] for the conversion of *ortho*-vanillin into pyrogallol monomethyl ether. The crude product (yield, 60—70%) distilled at 177°/16 mm., with no fore-run, but gave a precipitate with Brady's reagent. It was used without further purification. A cooled mixture of concentrated sulphuric acid (31 ml.) and water (50 ml.) was added to a solution of the crude quinol (53 g.) in water (250 ml.), and the whole run dropwise into a stirred solution of sodium dichromate (41 g.) in water (200 ml.) containing a little ice. More ice was added in small quantities during the oxidation. After all the methoxyquinol had been added, the solution (final volume *ca.* 800 ml.) was stirred for a further 15 min., then extracted with chloroform, and the extract dried (Na_2SO_4) and concentrated, to yield the yellow quinone (36 g., in two crops), m. p. 142° (lit., 145°).

*Michael Additions to Methoxy-*p*-benzoquinone.*—(a) *Diethyl malonate.* Method (1). Solutions of methoxy-*p*-benzoquinone (10 g.) in chloroform (100 ml.) dried by azeotropic distillation, and of diethyl sodiomalonate [made by dissolving sodium (1·6 g.) in anhydrous ethanol (100 ml.) and then adding malonic ester (7 ml.)] were separately cooled to −40°, mixed, and kept for 5—10 min. Liquid sulphur dioxide was sprayed in till the mixture became red and after 20 min., water (about 700 ml.) was added, and the mixture extracted with ether. The upper layer was separated and washed, first, with successive small quantities of sodium hydrogen carbonate solution until the washings, which were initially yellow, had changed through red, brown, and green, to blue, then with aqueous sulphur dioxide solution, finally repeatedly with water; it was then dried and evaporated, and a little benzene was added to the residue. Crystallisation was spontaneous and after recrystallisation from water, then from light petroleum (b. p. 100—102°), *diethyl* 2 : 5-*dihydroxy*-4-*methoxyphenylmalonate* had m. p. 137° (Found: C, 56·9; H, 6·1. $C_{14}H_{18}O_7$ requires C, 56·4; H, 6·0%). The yield was variable (0·5—3·5 g.), usually about 1·5 g.

Method (2). A solution of the quinone (1 g.) in absolute ethanol (100 ml.) containing diethyl malonate (2 ml.) was run down a column (12 × ½″) packed with glass beads, through which a current of ammoniacal air was drawn. The effluent was run into dilute acid (about

[4] Wood, Colburn, Cox, and Garland, *J. Amer. Chem. Soc.*, 1944, **66**, 1540.
[5] Fieser, *J. Amer. Chem. Soc.*, 1926, **48**, 2936.
[6] Erdtman, *Proc. Roy. Soc.*, 1934, *A*, **143**, 223.
[7] Surrey, in "Organic Syntheses," John Wiley & Sons, Inc., New York, 1955, Vol. III, p. 759.

XUM

500 ml.) through which a stream of sulphur dioxide was passed. After extraction with ether, working up was as described above (yield, 0·1—0·25 g.).

Slow chromatography of this ester in ether over alumina (grade II or III) caused partial conversion into the more strongly adsorbed lactone, *ethyl 5-hydroxy-6-methoxy-2-oxobenzofuran-3-carboxylate* (V), which crystallised from ether as rhombs, collapsing in air, m. p. 204° (decomp. from 180°) (Found: C, 56·7; H, 5·1. $C_{12}H_{12}O_6$ requires C, 57·1; H, 4·8%).

(b) *Dimethyl malonate.* Method (1) was followed, on half the scale, with methanol in place of ethanol. After evaporation of the solvents, the crude product was extracted from the residue with boiling ether–light petroleum (1 : 5 v/v), which left tar undissolved. Two experiments gave (i) 30 mg., (ii) no yield. Recrystallisation from ether–light petroleum gave *dimethyl 2 : 5-dihydroxy-4-methoxyphenylmalonate*, m. p. 139° (m. p. 115—117° on admixture with the diethyl ester) (Found: C, 53·1; H, 5·1. $C_{12}H_{14}O_7$ requires C, 53·3; H, 5·2%).

(c) *Ethyl cyanoacetate.* Method (1) was followed, on half the scale described in (a). After evaporation the ether-soluble portion of the residue was chromatographed over alumina (65 ml.; grade II). Unchanged ethyl cyanoacetate was followed by a fraction giving a blue colour with sodium carbonate solution, then by one giving a pink colour with this reagent. From the latter two fractions were isolated: (*a*) an oil and (*b*) crystals (0·08 g.) of *3 : 7-dicarbamoyl-2 : 6-diethoxybenzo*[1,2-*b* : 4,5-*b*']*difuran* (IX), m. p. 268° (decomp.) (Found: C, 58·3; H, 5·0; N, 8·5. $C_{16}H_{16}O_6N_2$ requires C, 57·8; H, 4·8; N, 8·4%). Acid-hydrolysis and then esterification with ethanolic hydrogen chloride gave 1 : 4-di(ethoxycarbonylmethyl)-2 : 5-dihydroxybenzene, m. p. 153° (Kofler block), identical (infrared spectrum) with an authentic sample, m. p. 153°. Treatment of the oil with ether–light petroleum gave (*inter alia*) crystals of *ethyl α-(3-carbamoyl-2-ethoxy-5-hydroxybenzo*[b]*fur-6-yl)-α-cyanoacetate* (X), m. p. 193—195°, solidifying and remelting at *ca.* 210° (decomp.) (Found: C, 58·3; H, 5·1; N, 8·7. $C_{16}H_{16}O_6N_2$ requires C, 57·8; H, 4·8; N, 8·4%). The compound gave an intense pink colour with 2N-sodium carbonate.

In another run, on the scale described, the ether-soluble products were chromatographed over alumina (40 ml.; grade III), and the fractions giving a blue colour with sodium carbonate solution collected and evaporated. The combined residues were recrystallised from ether–light petroleum (3 : 7, v/v), yielding *ethyl α-(2 : 5-dihydroxy-4-methoxyphenyl)-α-cyanoacetate* (Found: C, 57·7; H, 5·1; N, 5·7. $C_{12}H_{13}O_5N$ requires C, 57·5; H, 5·2; N, 5·6%). The compound had no definite m. p.; heated in a capillary tube, most of the crystals softened from about 110—120°, melting being complete between 140° and 150°, usually at 147°; however, isolated crystals on the wall of the tube melted completely at about 120°, resolidified at about 130°, and remelted at about 175°. Paper chromatography (acetic acid–butanol–water, 1 : 4 : 5) and exposure to ammonia vapour developed a single blue spot, R_F 0·92; spraying the alkaline paper with Folin–Ciocalteau reagent did not reveal any other spots, showing the absence of phenolic impurity.

Method (2). This experiment was done as described in section (a). Isolation of the product with ether and chromatography of the crude extract over alumina (30 ml.; grade III) gave the quinol (I; R = CO_2Et, R' = CN) (0·24 g.). In a repetition of this experiment, in which the mixture was set aside overnight before extraction with ether, the only product isolated was *2-ethoxy-5-hydroxy-6-methoxybenzofuran-3-carboxyamide* (VII) (0·33 g.), m. p. 173° (from benzene) (Found: C, 57·3; H, 5·2; N, 5·8. $C_{12}H_{13}O_5N$ requires C, 57·5; H, 5·2; N, 5·6%).

(d) *Malonodinitrile.* Using malonodinitrile (2·3 g.) and half quantities of the other reagents, as in (a), method (1), gave 0·6 g. of ether-soluble material. Chromatography of this in ether over alumina (60 ml.; grade III) gave *2 : 5-dihydroxy-4-methoxyphenylmalonodinitrile*, needles (from methyl cyanide), m. p. 233° (decomp.) (Found: C, 59·35; H, 4·3. $C_{10}H_8O_3N_2$ requires C, 58·8; H, 3·9%). The compound is very readily oxidised.

(e) *Ethyl acetoacetate.* Method (1) in section (a) was followed. After evaporation of the solvents, the residue was extracted with boiling light petroleum, then with ether. Concentration of the ether gave *ethyl 5-hydroxy-6-methoxy-2-methylbenzofuran-3-carboxylate*, prisms (from 95% ethanol), m. p. 160—161° (Found: C, 62·0; H, 5·5. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%). After evaporation of the petroleum, the residue was dissolved in ether; this ethereal solution gave a deep blue colour to sodium carbonate solution. After passage through alumina (100 ml.; grade III) the eluates gave only a weak blue colour to alkali, and contained a small quantity of the benzofuran (VI).

5-(Diethoxycarbonylmethyl)-2-methoxybenzoquinone.—The quinol (I; R = R' = CO_2Et) (0·4 g.) was dissolved in warm water (200 ml.) containing 1 drop of 0·1N-sulphuric acid and, after

being cooled, was added to a mixture of water (100 ml.), ice (300 g.), 0·1N-potassium dichromate (28 ml.), and N-sulphuric acid (4 ml.); after 40 min., the solution was extracted with ether, and the extract dried (Na_2SO_4), concentrated to about 20 ml., and run on a column of alumina (60 ml., grade II; this sample had not been exposed to sulphur dioxide). Development with ether caused a single, intensely purplish-brown band to move down the column, giving a yellow eluate. Evaporation of a portion of the eluate just behind the leading edge of the band left *5-(diethoxycarbonylmethyl)-2-methoxybenzoquinone* as a pale yellow oil (Found, in material dried at 100°/16 mm. for 2 hr.: C, 56·6; H, 5·4. $C_{14}H_{16}O_7$ requires C, 56·8; H, 5·4%). Treatment of the quinone with aqueous sulphur dioxide gave white crystals, m. p. 138° (mixed with the parent quinol, m. p. 137°).

Measurement of the Spectra for Table 1.—In those cases in which the quinols of type (I) were not isolated, solutions of the quinone (0·2%; 4 ml.) in absolute ethanol, the reactive methylene component (4 ml. in 10 ml. of 50% ethanol), and 5% sodium hydrogen carbonate solution (1 ml.) were mixed, and the spectra examined an a 2 mm. cell; with dimedone, 4 ml. of a 10% solution in absolute ethanol were used, in a 10 mm. cell. Many experiments had to be made to determine the position of $\lambda_{max.}$, because of the speed with which the colour faded.

This work was done during the tenure of an I.C.I. Fellowship, for which I thank this University.

THE UNIVERSITY, LEEDS, 2. [*Received, December 10th*, 1958.]

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432. *Chemical Constitution and Amœbicidal Action. Part III.* Synthesis of an Analogue of Emetine and Two Stereoisomers of De-ethylemetine.*

By M. BARASH and J. M. OSBOND.

An open chain analogue (VI) of emetine has been prepared as a potential amœbicide. A new route to de-ethylemetine (XV) has also been developed which has allowed the synthesis of two stereoisomers of this base.

ALTHOUGH challenged by antibiotics and a range of relatively simple compounds effective in varying degrees, emetine [1] (VII) is still [2] pre-eminent in the treatment of amœbiasis.[3] Many attempts to obtain simple analogues having the same or enhanced activity have so far not had practical success: [4] it appears that emetine is very specific. So we decided to prepare a close analogue, (VI), formally derived from emetine (VII) by fission of the bonds *a*–*a* and *b*–*b* and then to utilise one of the intermediates, (II), for synthesis of de-ethylemetine (XV).

The starting material, 3 : 4-dimethoxyphenethyl iodide, was prepared from 3 : 4-dimethoxybenzyl cyanide, obtained by chloromethylation of veratrole [5] or from veratraldehyde. Catalytic reduction of the aldehyde gave 3 : 4-dimethoxyphenethyl alcohol which was converted into the chloride and nitrile; the derived ethyl ester was reduced by lithium aluminium hydride to 3 : 4-dimethoxyphenethyl alcohol. Alternatively veratraldehdye was condensed with ethyl chloroacetate (Darzens reaction) to give ethyl 3 : 4-dimethoxyphenylglycidate; [6] alkaline hydrolysis gave the sodium salt, which with aqueous oxalic acid gave 3 : 4-dimethoxyphenylacetaldehyde [8] whence lithium aluminium hydride

* Part II, *J.*, 1952, 4785.

[1] See Janot, in Manske and Holmes's "The Alkaloids," Academic Press Inc., New York, 1953, Vol. III, p. 363.

[2] Rogers, *Brit. Med. J.*, 1912, I, 1424; 1912, II, 405.

[3] Woodruff, *Practitioner*, 1954, **173**, 441; "Treatment of Human Amœbiasis," *Trans. Roy. Soc. Trop. Med. Hyg.*, 1956, **50**, 109.

[4] Osbond, *J.*, 1951, 3461; Amin, Linnell, and Sharp, *J. Pharm. Pharmacol.*, 1957, **9**, 588.

[5] Bide and Wilkinson, *J. Soc. Chem. Ind.*, 1945, **84**; Gaivron, *J. Amer. Chem. Soc.*, 1949, **71**, 744.

[6] Cf. Henecka, *Annalen*, 1953, **583**, 126.

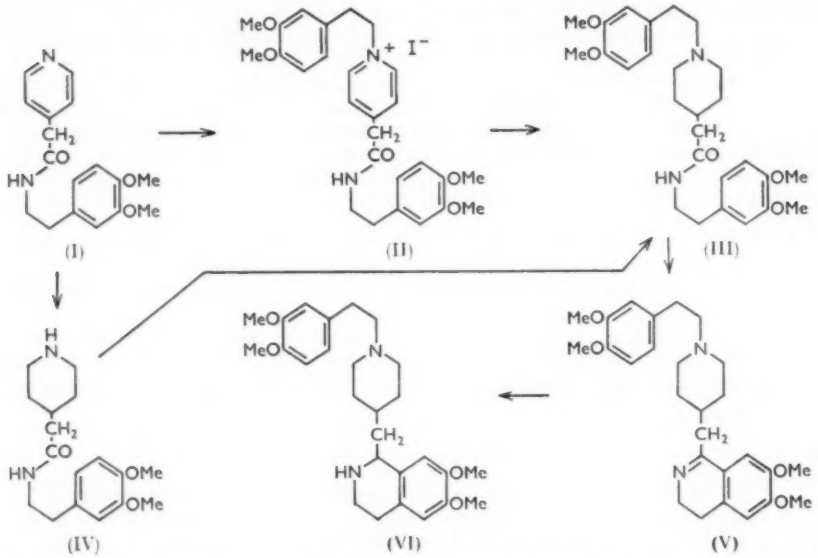
[7] Cf. Loftfield, *J. Amer. Chem. Soc.*, 1950, **72**, 2499; Shinya, *J. Agric. Chem. Soc. Japan*, 1950, **24**, 281; *Chem. Abs.*, 1953, **47**, 6374.

[8] Eliel, McBride, and Kaufmann, *J. Amer. Chem. Soc.*, 1953, **75**, 4293.

XUM

afforded the alcohol. The alcohol with thionyl chloride gave 3 : 4-dimethoxyphenethyl chloride and thence the iodide.

The other starting material, ethyl 4-pyridylacetate, was prepared either from 4-acetylpyridine [9] or from 4-vinylpyridine by the Kindler modification of the Willgerodt reaction [10] to give 4-4′-pyridyl(thioacetyl)morpholine (with some 4-ethylpyridine [11] and thioacetomorpholide). Alkaline hydrolysis of the morpholide gave the required acid which was



esterified without isolation. Condensing ethyl 4-pyridylacetate with 3 : 4-dimethoxyphenethylamine gave the amide (I). Quaternisation of this with 3 : 4-dimethoxyphenethyl iodide in methanol gave the iodide (II), but reaction in benzene or without solvent gave a non-crystalline product having part of its iodine in non-ionic form.[12] The quaternary salt was reduced catalytically to the piperidine base (III). This base was also prepared by the route (I) ⟶ (IV) ⟶ (III), which confirms its structure. In a third attempt quaternisation of the 3 : 4-dimethoxyphenethyl iodide and ethyl 4-pyridylacetate and reduction of the quaternary salt to ethyl 1-(3 : 4-dimethoxyphenethyl)-4-piperidylacetate was successful, but the final step, condensation with the phenethylamine, gave no crystalline product.

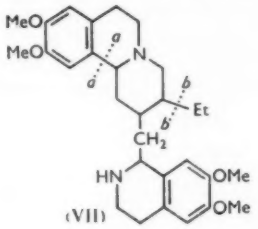
The base (III) was readily cyclised by phosphorus pentachloride in chloroform or by phosphorus oxychloride in toluene to the dihydro*iso*quinoline (V), hydrogenation of which gave the required tetrahydro*iso*quinoline (VI).

Although de-ethylemetine * (XV) has already been prepared four times,[13] it has not been evaluated for amœbicidal properties and only one stereoisomer has been isolated. The base (XV) contains three asymmetric centres, so four racemic stereoisomers are possible and might have interesting chemotherapeutic properties.

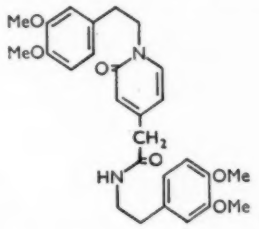
* The name bisnoremetine, previously used, is ambiguous as it could apply to emetine with 2OH replacing 2OMe. Ed.

[9] Malan and Dean, *J. Amer. Chem. Soc.*, 1947, **69**, 1797; Katritzky, *J.*, 1955, 2586.
[10] Noller and Wunderlich, *J. Amer. Chem. Soc.*, 1952, **74**, 3835.
[11] Cf. Fieser and Kilmer, *ibid.*, 1940, **62**, 1354.
[12] Cf. Hartwell and Kornberg, *ibid.*, 1946, **68**, 868; Kosower, *ibid.*, 1955, **77**, 3883.
[13] (*a*) Pailer, Schneglberger, and Reifschneider, *Monatsh.*, 1952, **83**, 513; (*b*) Pailer and Strohmayer, *ibid.*, 1952, **83**, 1198; (*c*) Tomimatsu, *J. Pharm. Soc. Japan*, 1953, **73**, 75; (*d*) Sugasawa and Oka, *Pharm. Bull.* (*Japan*), 1954, **2**, 85.

We first tried to oxidise the quaternary salt (II) by the well-known alkaline ferricyanide procedure [14] to the pyridone (VIII) which could by obvious methods be converted into de-ethylemetine (XV), but obtained only tars; there was a similar result in experiments with the simpler 1-(3 : 4-dimethoxyphenethyl)-4-picolinium iodide. Since



(VII)



(VIII)

this oxidation can be carried out with the 3-methylpyridinium salt [15] but not with the 2-methyl isomer [16] it appears that the reactive 2- or 4-methylene group is further oxidised possibly in the anhydro-base form. The pyridone (VIII) was later prepared by a different method [13d] and converted into de-ethylemetine.

Our second approach is shown in formulæ (IX) ⟶ (XV); we had in mind its adaptation to the synthesis of emetine. 4-Methyl-2-pyridone [16] with 3 : 4-dimethoxyphenethyl iodide in aqueous *tert.*-butyl alcohol containing potassium hydroxide gave the *N*-substituted pyridone (IX); although under alkaline conditions the *N*-alkylpyridone is normally obtained, there are several recorded cases [17] where *O*-alkylation is the chief reaction; so, to confirm the structure of our compound, 2-bromo-4-methylpyridine [18] was converted by 3 : 4-dimethoxyphenethyl iodide into a (non-crystalline) salt (XVII) which on mild alkaline hydrolysis [19] gave the identical pyridone (IX).

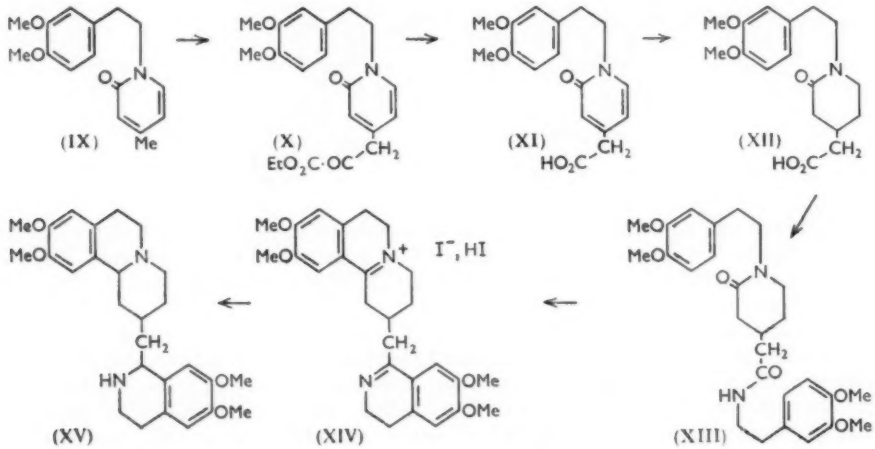
This pyridone with ethyl oxalate in the presence of potassium ethoxide [16,17,20] gave the pyruvate ester (X). Attempts to oxidise the pyruvate ester or its potassio-derivative by alkali and hydrogen peroxide together [16] were unsuccessful. It was necessary first to hydrolyse the ester with dilute alkali at 0° and then to add hydrogen peroxide which gave a good yield of the pyridone-acid (XI); a more convenient route was to use the potassio-derivative of the ester (X) in this reaction. From the mother-liquor of the oxidation a small amount of the 4-methyl-2-pyridone (IX) was isolated, presumably as a result of a reverse Claisen reaction.

The structure of the acid (XI) was proved in two ways. The ester (X) or its potassio-derivative with hydroxylamine hydrochloride gave the hydroxyimino-ester (XVIII), hydrolysed by alkali to the acid (XIX), which afforded the nitrile (XX) by pyrolysis or, preferably, on treatment with acetic anhydride.[21] Hydrolysis of the nitrile (XX) with dilute alkali yielded the acid (XI). Secondly, the acid (XI) at its decomposition point lost carbon dioxide and gave the 4-methyl-2-pyridone (IX); this behaviour is typical of 2- and 4-pyridylacetic acids and would be expected with a similar 2-pyridone-acid. The methyl ester of acid (XI) was prepared both from this acid by diazomethane or from the nitrile (XX) by methanolic hydrogen chloride. The piperidone-acid (XII) was obtained by catalytic reduction of the pyridone-acid by using Adams catalyst. The structure of the acid (XII) was proved by cyclising its methyl ester (XXI) in toluene with

[14] Thyagarajan, *Chem. Rev.*, 1958, **58**, 439; Sugasawa, Kodama, and Inagaki, *Ber.*, 1941, **74**, *B*, 455.
[15] Bradlow and VanderWerf, *J. Org. Chem.*, 1951, **16**, 73.
[16] Adams and Schrecker, *J. Amer. Chem. Soc.*, 1949, **71**, 1186.
[17] Leonard and Boyer, *ibid.*, 1950, **72**, 2980; Ramirez and Paul, *J. Org. Chem.*, 1954, **19**, 183.
[18] Lott and Shaw, *J. Amer. Chem. Soc.*, 1949, **71**, 70.
[19] Cf. VanderWerf and Bradlow, *J. Org. Chem.*, 1951, **16**, 1143.
[20] Kaslon and Cook, *J. Amer. Chem. Soc.*, 1945, **67**, 1969; Wislicenus, *Ber.*, 1909, **42**, 1141; Borsche and Manteuffel, *Annalen*, 1938, **526**, 22; Snyder and Williams, *J. Amer. Chem. Soc.*, 1954, **76**, 1298.
[21] Cf. Barnard and Bateman, *J.*, 1950, 926.

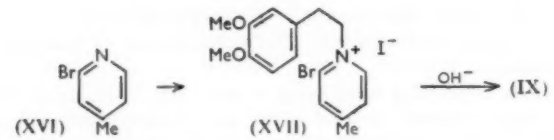
phosphorus oxychloride to the known 1 : 2 : 3 : 4 : 6 : 7-hexahydrobenzo[*a*]quinolizinium iodide [13b] (XXII), and the properties of the salt (XXII) agreed with those in the literature.

The triethylammonium salt of the 2-oxo-4-piperidylacetic acid (XII) in dimethylformamide with ethyl chloroformate gave, in the usual way,[22] the ethoxycarbonyloxy-derivative, which without isolation was treated with 3 : 4-dimethoxyphenethylamine in the



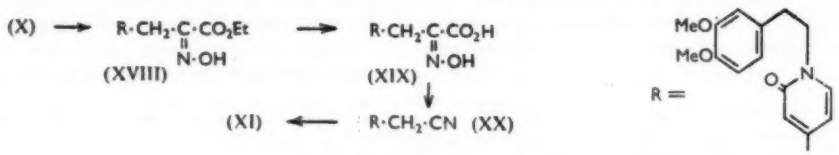
presence of triethylamine to give the amide (XIII) in two crystalline forms, m. p. 120—121° and m. p. 130—131°, which were interconvertible. This amide had previously been prepared by Tomitsu [13b] as a gum and, after our work was complete, Sugasawa and Oka [13d] reported it as having m. p. 130—131°.

Phosphorus oxychloride in toluene effected double ring closure of the amine (XIII) to the quaternary compound, characterised as the iodide hydriodide (XIV) and bromide



hydrobromide, both crystalline; the ultraviolet absorption spectrum was in agreement with this structure.

Catalytic reduction of the iodide hydriodide was slow but complete, and the first racemate of de-ethylemetine (XV; A) separated as a crystalline dihydriodide and afforded

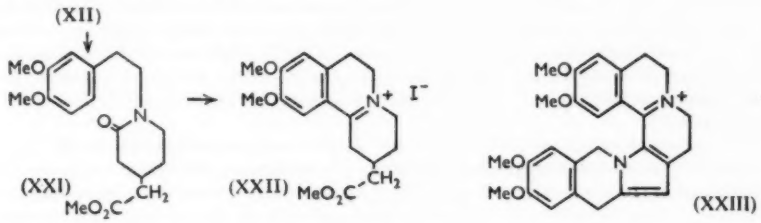


a dihydrobromide and dihydrogen dioxalate. The mother-liquors yielded a second isomer (XV; B), isolated as dihydrogen dioxalate and dihydrobromide. The structures of the

[22] Vaughan and Osato, *J. Amer. Chem. Soc.*, 1952, **74**, 676; Boissonnas, *Helv. Chim. Acta*, 1951, **34**, 874.

isomers were confirmed by the ultraviolet spectrum and dehydrogenation by mercuric acetate [23] of isomer B to de-ethylrubremetinium bromide (XXIII) as an orange-scarlet solid in good yield; it had the characteristic ultraviolet absorption [13b] (cf. rubremetinium bromide [24]).

Amœbicidal evaluation of these compounds was carried out on weanling rats infected with *E. histolytica*, by a modification of Jones's method.[25] Under standard conditions emetine has CD_{50} of 6·25—12·5 mg./kg.; by contrast, suitable hydrohalide salts of bases (V), (VI), (XIV), and (XV, A and B) were inactive at 250, 500, 5 × 100, 5 × 100, and 5 × 100 mg./kg., respectively.



Experimental

3 : 4-*Dimethoxybenzyl Alcohol*.—Veratraldehyde (120 g.; m. p. 43·5—45°) was hydrogenated in methanol in the presence of Raney nickel (*ca.* 10 g. in methanol) at 90° with an initial pressure of 50 atm., substantially completely in 2 hr. The mixture was cooled, filtered, and concentrated to a viscous oil which on distillation gave the alcohol (116 g., 95·5%), b. p. 112—120°/0·25—0·35 mm., n_D^{19} 1·5520.

3 : 4-*Dimethoxyphenylacetonitrile*.[27]—Thionyl chloride (17 c.c.) was added in 25 min. to 3 : 4-dimethoxybenzyl alcohol (25 g.) in benzene (20 c.c.) at 0°. After the initial reaction had subsided the benzene and thionyl chloride were removed under reduced pressure on the water-bath. The residue was refluxed in benzene (*ca.* 100 c.c.) with potassium cyanide (14·6 g.) in water (50 c.c.) for 2¾ hr. with stirring. The phases were separated and the aqueous phase was re-extracted with benzene. The benzene extracts were dried and distilled. The residue was distilled to give the nitrile (16·7 g., 63%), b. p. 128—130°/0·1—0·25 mm., m. p. 60—61°.

Ethyl **3 : 4-*Dimethoxyphenylacetate*.**—A solution of the above nitrile [5] (90 g.) in dry ethanol (500 c.c.) was saturated with hydrogen chloride, then cooled to 0°. The nitrile which separated gradually redissolved to give a purple solution. The mixture was kept at 0° overnight, then most of the alcohol was removed under reduced pressure at 35°. Dry ether was added to the residue and the crystalline *ethyl* **3 : 4-*dimethoxyphenylacetimidoate hydrochloride*** was collected and washed with dry ether; it recrystallised from cold ethanol–ether in prisms, m. p. 114·5—115° (Found: N, 5·7; Cl, 13·4. $C_{12}H_{18}O_3NCl$ requires N, 5·4; Cl, 13·7%). The salt was dissolved in water; after a few minutes at room temperature an oil separated and this was extracted with ether. The aqueous solution was then kept in contact with ether for 18 hr., the ether extracts being separated from time to time. The ether extracts were combined, washed with dilute sodium carbonate solution and with water, and dried (Na_2SO_4). The residue after removal of the ether was distilled, to give the ester (94·3 g., 83%), b. p. 132—136°/0·1—0·3 mm., n_D^{20} 1·5192 (Found: C, 64·5; H, 8·0. Calc. for $C_{12}H_{16}O_4$: C, 64·3; H, 7·2%).

Ethyl **3 : 4-*Dimethoxyphenylglycidate*.**—A mixture of 3 : 4-dimethoxybenzaldehyde (redistilled; 66·4 g.) and ethyl chloroacetate (redistilled; 41·3 c.c.) was added during 4 hr. to a stirred solution from sodium (9·4 g.) and absolute ethanol (133·2 c.c.) at −10°. Stirring was continued for a further 6 hr. at room temperature. After being kept at room temperature

[23] Battersby and Openshaw, *J.*, 1949, 567.
[24] Karrer, Eugster, and Ruttner, *Helv. Chim. Acta*, 1948, **31**, 1219.
[25] Jones, *Ann. Trop. Med. Parasitol*, 1956, **40**, 130.
[26] Bills and Noller, *J. Amer. Chem. Soc.*, 1948, **70**, 951.
[27] Livshits, Bainova, Bazilevskaya, Genkin, Preobrazhenskii, Rozanova, and Baranova, *Zhur. obshchei Khim.*, 1951, **21**, 1354.

overnight the mixture was poured on ice containing acetic acid (*ca.* 5 c.c.). The yellow solid was filtered and dried (P_2O_5; vac.). After several days a dry solid (81·5 g., 77·1%), m. p. 49—51°, was obtained. Crystallisation from ether–light petroleum (b. p. 40—60°) gave the *ester* as needles, m. p. 52·5—53·5° (Found: C, 62·1; H, 6·3. $C_{13}H_{16}O_5$ requires C, 61·8; H, 6·3%).

3 : 4-*Dimethoxyphenylacetaldehyde*.—The glycidic ester (12·6 g.) in ether (100 c.c.) was added in 15 min. to a solution from sodium (1·25 g.) in methanol (17 c.c.) and water (1 c.c.) at 5°. The mixture was kept at 0° for 19 hr., and ether (20 c.c.) added after 7 hr. The sodium 3 : 4-dimethoxyphenylglycidate (12·05 g., 98%) was collected and washed with ether. The salt (18·9 g.) was dissolved in water (75 c.c.) and added to oxalic acid (13·5 g.) in water (60 c.c.) at 95—100° with a rapid stream of nitrogen passing through the solution, during 15—20 min. The solution was then heated for a further 5 min., cooled, and extracted three times with chloroform. The chloroform extracts were washed with water and dried (Na_2SO_4). Distillation gave the pure aldehyde (8·6 g., 62%), b. p. 115—121°/0·7—1·0 mm., n_D^{20} 1·5430 (lit.,[28] n_D^{20} 1·5431) (Found: C, 66·3; H, 6·7. Calc. for $C_{10}H_{12}O_3$: C, 66·6; H, 6·7%). The 2 : 4-dinitrophenylhydrazone separated from ethyl acetate as orange-red needles, m. p. 168—169° (lit.,[28] m. p. 169—169·5°).

3 : 4-*Dimethoxyphenethyl Alcohol*.—(1) Ethyl 3 : 4-dimethoxyphenylacetate (33·6 g.) in dry ether (150 c.c.) was added dropwise with stirring to a suspension of lithium aluminium hydride (7·5 g.) in dry ether (150 c.c.); after 0·5 hour's heating on a water-bath a fairly granular precipitate was obtained. Ethyl acetate (25 c.c.) was added, followed by 2N-sulphuric acid (excess) with ice-cooling. The aqueous phase was extracted with ether six times, the combined extracts were washed with sodium carbonate solution, dried, and evaporated. Distillation gave the alcohol (25·2 g., 92%), b. p. 126—128°/0·3—0·7 mm., m. p. 45—46·5° (lit.,[29] m. p. 48°) (Found: C, 66·4; H, 8·2. Calc. for $C_{10}H_{14}O_3$: C, 65·9; H, 7·7%). The *toluene-p-sulphonate*, prepared in pyridine at 0—5°, separated from ether–light petroleum and had m. p. 49—51·5° (1·04 g. from 1·82 g.) (Found: C, 60·9; H, 6·1; S, 9·4. $C_{17}H_{20}O_5S$ requires C, 60·7; H, 6·0; S, 9·5%).

(2) 3 : 4-Dimethoxyphenylacetaldehyde (8·63 g.) was reduced by lithium aluminium hydride (2 g.) in ether (100 c.c.), as above, to the alcohol (6·6 g., 75%), b. p. 112—118°/0·3 mm., m. p. 41—43°.

3 : 4-*Dimethoxyphenethyl Chloride*.—Thionyl chloride (8·92 g., 0·075 mole) in dry benzene (15 c.c.) was added with stirring to a solution of 3 : 4-dimethoxyphenethyl alcohol (9·1 g., 0·05 mole) and diethylaniline (7·93 c.c., 0·05 mole) in benzene (60 c.c.) during 0·5 hr. The mixture was kept at room temperature for 1·5 hr., then heated on a boiling-water bath for 10 min. Two-thirds of the benzene was removed under reduced pressure and the resulting solution was washed with water, dilute aqueous sodium carbonate, and water, dried (Na_2SO_4), and evaporated. Distillation of the residue gave the chloro-compound (9·45 g., 94%), b. p. 126°/0·3 mm., laths, m. p. 37·5—39·5° [from ether–light petroleum (b. p. 40—60°) at −15°] (Found: C, 59·8; H, 6·7; Cl, 17·3. Calc. for $C_{10}H_{13}O_2Cl$: C, 59·9; H, 6·5; Cl, 17·7%).

3 : 4-*Dimethoxyphenethyl Iodide*.—(1) Sodium iodide (132 g.; dry and powdered) was refluxed in dry ethyl methyl ketone (1 l.) for 1·5 hr. The mixture was then cooled, 3 : 4-dimethoxyphenethyl chloride (117 g.) in dry ethyl methyl ketone (200 c.c.) was added, and the mixture refluxed for a further 10 hr. Precipitated sodium chloride was removed, most of the ketone was distilled off, and the residue was dissolved in ether and water. The aqueous layer was extracted six times with ether and washed with sodium thiosulphate solution and water. The ether extract was dried and evaporated and the residue distilled, to give the iodo-compound (157 g., 92%), b. p. 112°/0·3 mm., prisms, m. p. 45—47° [from ether–light petroleum (b. p. 40—60°)] (Found: I, 42·9. Calc. for $C_{10}H_{13}O_2I$: I, 43·4%).

(2) 3 : 4-Dimethoxyphenethyl toluene-*p*-sulphonate (1·68 g.) was refluxed in dry acetone (25 c.c.) with sodium iodide (0·82 g.) for 3 hr. The sodium toluene-*p*-sulphonate (0·92 g.) was filtered off and the acetone was removed under reduced pressure, and the product was obtained as in (1), having m. p. and mixed m. p. 45·5—48°.

4-4′-*Pyridyl(thioacetyl)morpholine*.—Redistilled 4-vinylpyridine (10·5 g., 0·1 mole), sulphur (4·8 g., 0·15 mole), and morpholine (13·0 g., 0·15 mole) were refluxed at 160° for 16 hr. The resultant dark mass was dissolved in ethanol (15 c.c.) and cooled to 0°. The morpholide (11·83 g., 53%) was collected and recrystallised from ethanol as yellow prisms, m. p. 105—107°

[28] Kaufmann, Eliel, and Rosenkrantz, *Ciencia (Mexico)*, 1946, **7**, 136; Scopf, Gottman, Meisel, and Neuroth, *Annalen*, 1949, **563**, 86.

[29] Brace, *J. Amer. Chem. Soc.*, 1953, **75**, 357.

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(lit.,[9] m. p. 104—105·5°). The alcoholic mother-liquor was basified with aqueous potassium hydroxide and extracted 6 times with ether. Distillation of the ether-soluble material gave 4-ethylpyridine (1·35 g.), b. p. 50°/12 mm., n_D^{20} 1·4988 (lit., 1·5022) [picrate, m. p. and mixed m. p. 167—169° (from alcohol)], and thioacetomorpholide (0·6 g.), b. p. 143—146°/12 mm., m. p. 90—92° (lit.,[29] m. p. 89—91·2°) (Found: C, 49·7; H, 7·8; N, 9·6; S, 22·1. Calc. for $C_6H_{11}ONS$: C, 49·6; H, 7·6; N, 9·6; S, 22·0%).

Ethyl 4-Pyridylacetate.—4-4′-Pyridyl(thioacetylmorpholine (33·3 g., 0·15 mole) was refluxed with potassium hydroxide (23 g.) in alcohol (180 c.c.) for 16 hr. Water (360 c.c.) was added and the solution concentrated to half-volume under reduced pressure; then water (180 c.c.) was added and the solution was evaporated nearly to dryness, made just acid with 2N-hydrochloric acid, evaporated to dryness, and co-distilled with ethanol (twice) and benzene. The dry residue was suspended in absolute ethanol (200 c.c.), saturated with hydrogen chloride without cooling, and kept overnight at room temperature. The alcohol was removed and dilute sodium carbonate and ether were added. The residue from the ether-extracts was distilled, to give the ester (18·9 g., 76%), b. p. 86—90°/0·2—0·4 mm. The *hydrochloride* separates from ethanol as prisms, m. p. 165—168° (decomp.) (Found: C, 54·0; H, 6·1; N, 6·9. $C_9H_{12}O_2NCl$ requires C, 53·7; H, 6·0; N, 6·9%).

Ethyl 1-(3 : 4-Dimethoxyphenethyl)-4-piperidylacetate.—3 : 4-Dimethoxyphenethyl iodide (2·92 g.) and ethyl 4-pyridylacetate (1·65 g.) were heated on a boiling-water bath for 2 hr., to give a quaternary salt which was hydrogenated in ethanol (60 c.c.) and triethylamine (1·6 c.c.) and at 145—150°/75 atm. for 3 hr. in the presence of Raney nickel. The product after removal of the alcohol was treated with excess of 2N-sodium carbonate, and extracted with ether three times. The extract was dried (Na_2SO_4) and distilled (b. p. 188—192°/0·6 mm.; 1·16 g.), affording the *product* which after several recrystallisations from ether–light petroleum (b. p. 40—60°) at −20° formed prisms, m. p. 38·5—40° (Found: C, 68·4; H, 8·9; N, 3·8. $C_{19}H_{29}O_4N$ requires C, 68·0; H, 8·7; N, 4·2%).

N-(3 : 4-Dimethoxyphenethyl)-α-4-pyridylacetamide (I).—3 : 4-Dimethoxyphenethylamine (9·05 g.), ethyl 4-pyridylacetate (8·25 g.), and a few drops of dry pyridine were heated at 180° for 3 hr., then dissolved in benzene from which the crude amide (11·3 g., 75%) separated. Recrystallisation from benzene gave the *amide* (10·5 g.) as needles, m. p. 93·5—95° (Found: C, 68·3; H, 7·3; N, 9·2. $C_{17}H_{20}O_3N_2$ requires C, 68·0; H, 6·7; N, 9·3%).

N-(3 : 4-Dimethoxyphenethyl)-α-4-piperidylacetamide (IV).—The foregoing amide (3 g.) was shaken in ethanol (40 c.c.) with Raney nickel for 1½ hr. The suspension was filtered and the nickel was washed with glacial acetic acid. Further acetic acid (60 c.c.) was added to the filtrate which was then hydrogenated in the presence of Adams catalyst. The product after removal of solvent was partitioned between dilute sodium carbonate and chloroform. Several chloroform extracts were obtained, washed with water, and dried (Na_2SO_4). The solid residue crystallised from benzene–light petroleum (b. p. 40—60°), to give the *amide* (1·72 g.), m. p. 93—96°, needles (Found: C, 67·0; H, 8·4; N, 8·8. $C_{17}H_{26}O_3N_2$ requires C, 66·6; H, 8·5; N, 9·1%).

1-(3 : 4-Dimethoxyphenethyl)-4-[N-(3 : 4-dimethoxyphenethyl)carbamoylmethyl]pyridinium Iodide (II).—3 : 4-Dimethoxyphenethyl iodide (2·92 g.) and *N*-(3 : 4-dimethoxyphenethyl)-α-4-pyridylacetamide (3·0 g.) were refluxed in absolute methanol (25 c.c.) in nitrogen for 16 hr. After concentration of the solution to *ca.* 10 c.c. the quaternary salt (4·87 g.), m. p. 142—146°, slowly separated. Recrystallisation from absolute ethanol gave the *pyridinium iodide*, m. p. 146—148° (softens at 145°), as yellow prisms (Found: C, 53·4, 53·7; H, 6·0, 6·0; I′, 22·2, 22·2. $C_{27}H_{33}O_5N_2I,H_2O$ requires C, 53·1; H, 5·8; I′, 20·8%).

N-(3 : 4-Dimethoxyphenethyl)-α-(3 : 4-dimethoxyphenethyl-4-piperidyl)acetamide (III).—(1) The iodide (II) (11·85 g.) in methanol (300 c.c.) was hydrogenated at atmospheric pressure and room temperature in the presence of Adams catalyst (0·5 g.) (uptake 1560 c.c.; theor., 1555 c.c.). The solution was filtered, concentrated, and basified with 2N-sodium hydroxide, and the base extracted with chloroform (5 times). The recovered *base* (8·25 g., 88%) separated from ethyl acetate as needles, m. p. 135·5—136° (Found: C, 68·8; H, 8·0; N, 6·1. $C_{27}H_{38}O_5N_2$ requires C, 68·9; H, 8·1; N, 5·9%).

3 : 4-Dimethoxyphenethyl iodide (0·73 g.), the amide (IV), and potassium carbonate (0·52 g.) were refluxed in dry benzene (20 c.c.) for 3 hr. The solution was washed with water and evaporated. The residual solid crystallised from ethyl acetate, to give the amide (II) (0·6 g.), m. p. and mixed m. p. 133—135·5° (from ethyl acetate).

4-(3 : 4-Dihydro-6 : 7-dimethoxy-1-isoquinolylmethyl)-1-(3 : 4-dimethoxyphenethyl)piperidine

(V).—(i) Phosphorus pentachloride (3 g.) was added to the amide (III) (2·46 g.) in dry chloroform (30 c.c.) at 5°. The mixture was kept at 0° for 0·5 hr. with intermittent shaking, then at room temperature for 18 hr. Most of the chloroform was removed under reduced pressure and ice and excess of 2N-sodium hydroxide were added. The basic material was extracted with chloroform, washed with water, and recovered. The residue dissolved in warm ether and after removal of some flocculent material was recovered as an oil. Dilute hydrochloric acid was added, and the yellow solution evaporated to a yellow foam. After distillation of the residue 3 times with alcohol it was dissolved in ethanol to which ether was added. The *dihydrochloride* separated as yellow prisms (2·42 g., 88%), m. p. 105—110°. Recrystallisation from ethanol–ether with a trace of dry hydrogen chloride gave pale yellow prisms which, after drying at 50—60° *in vacuo*, had m. p. ~180—185° (softening at 160°, doubtless owing to hydration). The salt was very hygroscopic and its dilute ethanolic solution had a bright blue fluorescence (Found: C, 59·9; H, 7·1; N, 5·2. $C_{27}H_{36}O_4N_2,2HCl,H_2O$ requires C, 59·7; H, 7·4; N, 5·1%).

The *dihydrobromide* was less hygroscopic and crystallised from ethanol as pale yellow prisms, m. p. (air-dried) m. p. 131—136° (meniscus and frothing at 155—160°) (Found: C, 48·1, 48·3; H, 6·2, 6·6; N, 3·9; Br, 23·9; H_2O, 10·2. $C_{27}H_{36}O_4N_2,2HBr,3H_2O$ requires C, 48·5; H, 6·6; N, 4·2; Br, 23·9; H_2O, 8·1%).

The *base*, crystallised from light petroleum (b. p. 60—80°) containing a few drops of ether, had m. p. 99—102·5° (Found: C, 71·8; H, 8·4; N, 5·8. $C_{27}H_{36}O_4N_2$ requires C, 71·6; H, 8·0; N, 6·2%).

(ii) The amide (III) (2·35 g.) was refluxed in dry toluene (15 c.c.) and phosphorus oxychloride (10 c.c.) for 1 hr., cooled, washed by decantation with light petroleum (b. p. 60—80°), and dissolved in aqueous alcohol. Excess of 50% sodium hydroxide solution was added and the basic material extracted with ether (3 times) and washed with water. The recovered base was converted into the dihydrobromide which separated from ethanol as yellow prisms (2·32 g., 75%), m. p. (air-dried) and mixed m. p. 131—136°.

1-(3 : 4-*Dimethoxyphenethyl*)-4-(1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-1-iso*quinolylmethyl*)-*piperidine* (VI).—The dihydrobromide (V) (3·07 g.) was hydrogenated at room temperature and atmospheric pressure in methanol (50 c.c.) with Adams catalyst (0·2 g.). The filtered solution was concentrated to 25—30 c.c. and treated with hydrobromic acid, to give a dihydrobromide (2·55 g., 92%), m. p. 188—192°. Recrystallisation from methanol gave the *tetrahydroisoquinoline dihydrobromide* as prisms, m. p. (air-dried) 190—196° (Found: C, 50·3; H, 6·6; N, 4·5; Br, 24·2; H_2O, 5·1. $C_{27}H_{38}O_4N_2,2HBr,2H_2O$ requires C, 49·7; H, 6·80; N, 4·3; Br, 24·5; H_2O, 5·5. Found, in a sample dried at 90° *in vacuo*: loss, H_2O, 2·5; C, 51·9; H, 6·4. $C_{27}H_{38}O_4N_2,2HBr,H_2O$ requires H_2O, 2·8; C, 51·1; H, 6·7%).

In a preliminary reduction the tetrahydro*iso*quinoline was isolated as the *dihydrogen dioxalate*, needles (from methanol–ether), m. p. 173·5—175° (decomp. 180—185°) (Found: C, 58·2; H, 6·8; N, 4·7. $C_{27}H_{38}O_4N_2,2H_2C_2O_4$ requires C, 58·6; H, 6·7; N, 4·4%).

1-(3 : 4-*Dimethoxyphenethyl*)-4-*picolinium Iodide*.—3 : 4-Dimethoxyphenethyl iodide (2·92 g.) and γ-picoline (0·93 g.) were heated on a boiling-water bath for 2 hr. The crystalline precipitate was dissolved in ethanol from which the quaternary *salt* separated as yellow needles (6·6 g.), m. p. 184—187° (Found: C, 50·2; H, 5·3; N, 3·6. $C_{16}H_{20}O_2NI$ requires C, 49·9; H, 5·2; N, 3·6%).

1-(3 : 4-*Dimethoxyphenethyl*)-4-*methyl*-2-*pyridone Hydrochloride* (IX).—(i) To potassium hydroxide (6·6 g.), dissolved in water (3 c.c.) and *tert.*-butyl alcohol (80 c.c.), 4-methyl-2-pyridone (10·9 g., 0·1 mole) was added and the solution was heated for a few minutes to obtain complete dissolution. 3 : 4-Dimethoxyphenethyl iodide (29·2 g., 0·1 mole) was added and the solution was refluxed for 2·75 hr. The solvent was then removed and the residue was partitioned between benzene and 2N-sodium hydroxide. The aqueous layer was extracted 3 times with benzene which was then removed, and the residue was dissolved in a very small volume of ethanol and treated with excess of ether saturated with dry hydrogen chloride. The *hydrochloride* (24·45 g., 79%) recrystallised from ethanol–ether as needles, m. p. 170—172° (Found: C, 62·6; H, 6·8; N, 4·5. $C_{16}H_{19}O_3N,HCl$ requires C, 62·0; H, 6·2; N, 4·5%).

(ii) 4-Methyl-2-pyridone (5·45 g.) was warmed with a solution from potassium (1·95 g.) and *tert.*-butyl alcohol (40 c.c.) for a few minutes, 3 : 4-dimethoxyphenethyl chloride (11·1 g.) was added, the whole refluxed for 6 hr., and the product obtained as described above as the hydrochloride (11·09 g., 71·6%) m. p. 165—166°.

(iii) 3 : 4-Dimethoxyphenethyl iodide (5·84 g.) and 2-bromo-4-methylpyridine were heated

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on a boiling-water bath for 5 hr. The residue was lixiviated with dry ether, dissolved in aqueous ethanol, treated with excess of 2N-sodium hydroxide at room temperature, and kept overnight. The solution was extracted with chloroform, dried, and evaporated. The residue gave on distillation a fraction (1·4 g.), b. p. 200—202°/0·5 mm., which gave the pyridone hydrochloride, m. p. 165—169°, when treated with ether saturated with dry hydrogen chloride. Recrystallisation gave the pure hydrochloride, m. p. 169—172°, identical with the compound prepared as above (Found: Cl, 11·4. $C_{16}H_{19}O_3N$,HCl requires Cl, 11·4%).

Ethyl 1-(3 : 4-*Dimethoxyphenethyl*)-1 : 2-*dihydro*-2-*oxo*-4-*pyridylpyruvate* (X).—Absolute ethanol (16·6 c.c.) was added to potassium (2·53 g.) under dry ether (14·4 c.c.), and dissolution completed by warming. Ethyl oxalate (9·48 g.) in ether (60 c.c.) was added dropwise at *ca.* 10°. After 10 min. 1-(3 : 4-dimethoxyphenethyl)-4-methyl-2-pyridone [from the hydrochloride (18·6 g.)] in benzene (90 c.c.) was added dropwise in 8 min. at 0°. After 2 days an oil separated which became solid on addition of ether (*ca.* 90 c.c.). This yellow potassio-derivative salt (19·0 g.) was filtered off after 4 days and washed with dry ether. From the filtrate a further 3·8 g. (total 91·2%) were obtained.

The potassio-derivative (10·3 g.) was added portionwise to 2N-sulphuric acid (32·5 c.c.), ice (17 g.) and chloroform (55 c.c.) with vigorous shaking. The chloroform was separated and the aqueous layer was re-extracted with chloroform; this was repeated again after adjustment of the pH of the aqueous extract to pH 7 with dilute ammonia. The combined extracts yielded the solid *pyruvate* which crystallised twice from ethanol or ethyl acetate as pale yellow prisms (7·9 g., 85% yield from potassio-derivative), m. p. 157—158·5° (Found: C, 64·5; H, 6·3; N, 3·4. $C_{20}H_{23}O_6N$ requires C, 64·3; H, 6·2; N, 3·7%).

Ethyl β-[1-(3 : 4-*Dimethoxyphenethyl*)-1 : 2-*dihydro*-2-*oxo*-4-*pyridyl*]-α-*hydroxyiminopropionate* (XVIII).—(i) The pyruvate (X) (3·73 g.) in alcohol (45 c.c.) was refluxed with hydroxylamine hydrochloride (0·77 g.) and anhydrous sodium acetate (0·88 g.) for 0·5 hr.; the solution was cooled and water (5 c.c.) added. The *oxime* (3·17 g., 82%), recrystallised from alcohol, had m. p. 186·5—189·5° (Found: C, 61·1; H, 6·3; N, 7·2. $C_{20}H_{24}O_6N_2$ requires C, 61·8; H, 6·2; N, 7·2%).

(ii) The crude potassio-derivative (3·8 g.) in alcohol (45 c.c.) was refluxed with hydroxylamine hydrochloride (0·77 g.) and sodium acetate (0·88 g.) for 0·5 hr., then concentrated to half its volume. The oxime (2·08 g., 58%) had m. p. and mixed m. p. 182—184°.

This ester (3·17 g.) was converted by 2N-sodium hydroxide (12·5 c.c.) on a boiling-water bath in 1·5 hr. into the *acid*, needles, m. p. 166—168° (2·50 g., crude) (Found: C, 59·9; H, 5·8; N, 7·8. $C_{18}H_{20}O_6N_2$ requires C, 60·0; H, 5·6; N, 7·8%).

1-(3 : 4-*Dimethoxyphenethyl*)-1 : 2-*dihydro*-2-*oxo*-4-*pyridylacetonitrile* (XX).—The hydroxyimino-acid (2·76 g.) was heated in acetic anhydride (5 c.c.) on a water-bath for 10 min., the anhydride removed under reduced pressure, and ethanol was added and then removed under reduced pressure. The crystalline *nitrile* was precipitated from a small volume of benzene by a few drops of light petroleum (b. p. 60—80°) as needles (1·82 g., 80%), m. p. 118—121° (Found: C, 68·4; H, 6·1; N, 10·0. $C_{17}H_{18}O_3N_2$ requires C, 68·4; H, 6·1; N, 9·4%).

1-(3 : 4-*Dimethoxyphenethyl*)-1 : 2-*dihydro*-2-*oxo*-4-*pyridylacetic Acid* (XI).—(i) The acetonitrile (0·23 g.) was refluxed overnight with ethanol (10 c.c.) and 2N-sodium hydroxide (5 c.c.). The alcohol was then removed and the aqueous alkaline solution extracted with benzene and then filtered. The filtrate was made acid by concentrated hydrochloric acid, and the precipitated red oil extracted with chloroform. After removal of the solvent the residue was dissolved in methanol from which prisms (0·23 g.), m. p. 158—161° (decomp.), were deposited. Crystallisation from methanol gave the *acetic acid*, m. p. 156·5—157° (decomp.) (Found: C, 64·3; H, 6·1; N, 4·7. $C_{17}H_{19}O_5N$ requires C, 64·3; H, 6·0; N, 4·4%).

(ii) The ester (X) (6·5 g.) was kept in 10% aqueous sodium hydroxide (31·2 c.c.) at 0° for 4·5 hr., then treated with 30% hydrogen peroxide (6·05 c.c.) and ice (*ca.* 17 g.) and kept for a further 16 hr. at 0°. Thereafter a further 2·6 c.c. of hydrogen peroxide were added and the solution was kept at 0° for a further 24 hr. Manganese dioxide (*ca.* 1 g.) was added, the solution filtered, and the filtrate made just acid to Congo-Red paper with concentrated hydrochloric acid. The oil was extracted with chloroform (3 × 25 c.c.), washed with water, and evaporated. The colourless solid residue was dissolved in methanol from which the acid (4·36 g., 78%), m. p. and mixed m. p. 157° (decomp.), separated.

(iii) The potassio-derivative (5·15 g.) was kept in 10% aqueous sodium hydroxide (22·5 c.c.) at 0° for 17 hr. Ice (12·5 g.) and 30% hydrogen peroxide (4·4 c.c.) were added and the solution

kept at 0° for 24 hr. A further 1·88 c.c. of hydrogen peroxide were added and the solution left for 3 days longer at 0°, then worked up as in (ii), to give the acid (2·91 g., 73·5%), m. p. 152—156° (decomp.). This reaction was repeated with the potassio-derivative (51·5 g.); after removal of the pyridylacetic acid (28 g.) the mother-liquor was concentrated to a syrup and treated with ethereal hydrogen chloride. The partially crystalline hydrochloride, after recrystallisation, gave 4-methyl-2-pyridone hydrochloride (3 g.), m. p. and mixed m. p. 166—167°.

Methyl 1-(3 : 4-*Dimethoxyphenethyl*)-1 : 2-*dihydro*-2-*oxo*-4-*pyridylacetate*.—(i) The nitrile (XX) (1·49 g.), suspended in dry methanol, was saturated at 0° with hydrogen chloride. After 20 hr. at 0° the methanol was removed under reduced pressure, and the residue dissolved in chloroform, washed with 2N-sodium carbonate, and evaporated. The residual ester was treated in a small volume of methanol with ethereal hydrogen chloride, which precipitated a slightly hygroscopic hydrochloride (1·37 g., 74%). Two recrystallisations from methanol–ether with a trace of dry hydrogen chloride gave the pure *hydrochloride*, m. p. 116·5—120° (Found: N, 4·3. $C_{18}H_{22}O_5NCl$ requires N, 3·8%). The hydrochloride in water dissociated to an oil; basification (2N-sodium carbonate) and extraction with chloroform gave the free *ester* which separated from benzene–light petroleum (b. p. 40—60°) as needles, m. p. 64·5—67° (from ether at −10°) (Found: C, 64·9; H, 6·4; N, 4·7. $C_{18}H_{21}O_5N$ requires C, 65·3; H, 6·4; N, 4·2%).

(ii) The acid (XI) (0·63 g.) was treated in methanol (3 c.c.) with ethereal diazomethane [from methylnitrosourea (1·17 g.)]. Next morning unchanged acid (0·133 g.) was filtered off and the ester converted by ethereal hydrogen chloride into the hydrochloride, m. p. and mixed m. p. 117—120°. The base had m. p. and mixed m. p. 67—69°.

1-(3 : 4-*Dimethoxyphenethyl*)-2-*oxo*-4-*piperidylacetic Acid* (XII).—The acid (XI) (4·76 g.) was hydrogenated in methanol (140 c.c.) at room temperature and pressure in the presence of Adams catalyst (0·2 g.). (Uptake in 24 hr., 820 c.c. Theor., at 23°/757 mm., 797 c.c.) The catalyst was removed and the filtrate concentrated to *ca.* 20 c.c. to which ether (*ca.* 100 c.c.) was added. The *piperidylacetic acid* (4·13 g., 86%), m. p. 146—148°, separated from methanol–ether in prisms, m. p. 147·5—149·5° (Found: C, 63·4; H, 7·4; N, 4·6. $C_{17}H_{23}O_5N$ requires C, 63·5; H, 7·2; N, 4·4%).

1 : 2 : 3 : 4 : 6 : 7-*Hexahydro*-9 : 10-*dimethoxy*-2-*methoxycarbonylmethylbenzo*[a]*quinolizinium Iodide* (XXII).—The acid (XII) (0·23 g.) was dissolved in warm methanol (20 c.c.), and hydrogen chloride was passed into the solution to saturation at 0°. The solution was kept at room temperature overnight, then the solvent was removed. The residue was dissolved in chloroform and washed with 2N-sodium carbonate and water. Removal of the solvent gave the oily methyl ester (XXI). Without being crystallised (Pailer and Strohmayer [13b] record m. p. 57—58°) this was cyclised by phosphorus oxychloride (1 c.c.) and toluene (4 c.c.) at 95° for 5—10 min. The iodide was isolated as described by Pailer and Strohmayer and crystallised from water as yellow needles, m. p. 218—219·5° (lit., 218—220°) (Found: C, 48·5; H, 5·5; N, 2·9. Calc. for $C_{18}H_{24}O_4NI$: C, 48·5; H, 5·4; N, 3·1%), $\lambda_{max.}$ 232 (log ε 4·29), 300 (log ε 3·96), and 245 mμ (log ε 3·97) in water.

1-(3 : 4-*Dimethoxyphenylethyl*)-4-N-(3 : 4-*dimethoxyphenethyl*)*carbamoylmethyl*-2-*oxopiperidine* (XIII).—Ethyl chloroformate (1·19 g.) was added to a solution of the acid (XII) (3·21 g.) and triethylamine (1·01 g.) in dry dimethylformamide (12·5 c.c.) at −15° to −20° during 10—15 min. The mixture was kept at −10° for 10 min., then allowed to warm to 0° for 10 min., cooled to −5°, treated with 3 : 4-dimethoxyphenethylamine (2·71 g.) and triethylamine (1·01 g.) in dimethylformamide (5 c.c.), kept at room temperature overnight, and evaporated. The residue was dissolved in chloroform and washed with 2N-hydrochloric acid (20 c.c.), 2N-sodium carbonate (20 c.c.), and water. The chloroform was removed and the residue dissolved in ethyl acetate. The amide (4·05 g., 84%), m. p. 126—128°, separated in needles on cooling and an analytical sample, obtained from ethyl acetate, had m. p. 120—121° or 130—131°; these forms are interconvertible (Found: C, 67·3; H, 7·6; N, 5·9. Calc. for $C_{27}H_{36}O_6N_2$: C, 66·9; H, 7·5; N, 5·8%). Sugasawa and Oka [13c] give m. p. 130—131°.

2-(3 : 4-*Dihydro*-6 : 7-*dimethoxy*-2-isoquinolylmethyl)-1 : 2 : 3 : 4 : 6 : 7-*hexahydro*-9 : 10-*dimethoxybenzo*[a]*quinolizinium Iodide Hydriodide* (XIV).—The amide (XIII) (9·70 g.) was heated in dry toluene (80 c.c.) with phosphorus oxychloride (20 c.c.) at 95° for 0·5 hr. Toluene and excess of phosphorus oxychloride were then removed and the residue was washed twice with dry light petroleum (b. p. 60—80°) by decantation. The residue was dissolved in water (100 c.c.) and a few c.c. were distilled under reduced pressure. On cooling, a small amount of crystalline material, m. p. 150°, was removed and, to the filtrate, sodium acetate (*ca.* 30 g.) and

XUM

then sodium iodide (24 g.) in water (40 c.c.) were added. The precipitated red oil was extracted with chloroform and washed with water. The recovered red gum was dissolved in methanol (*ca.* 60 c.c.) from which the *iodide hydriodide* (12·1 g., 85%), m. p. 193—195° (softens at 170°), separated; recrystallisation from methanol gave material of m. p. 193—195° (Found, in a sample dried at 60° *in vacuo*: C, 44·9; H, 5·0; N, 3·7; I, 36·0. $C_{27}H_{33}O_4N_2I,HI,H_2O$ requires C, 44·9; H, 5·0; N, 3·9; I, 35·1%). An air-dried sample had an indistinct m. p. (90—195°) owing to hydration (Found: C, 44·0; H, 5·1; N, 3·2. $C_{27}H_{33}O_4N_2I,HI,2H_2O$ requires C, 43·8; H, 4·9; N, 3·8%): at 100° *in vacuo* (2 hr.) it lost one molecule (Found: loss, 2·9. $C_{27}H_{33}O_4N_2I,HI,2H_2O$ requires H_2O, 2·4%). The absorption spectrum (solution in water) had maxima at 227·5 (log ε 4·61), 302·5 (log ε 4·29), and 455 mμ (log ε 4·29).

Use of sodium bromide instead of sodium iodide gave the *bromide hydrobromide*, pale yellow prisms, m. p. 193—195° (from methanol–ether) (Found: C, 50·2; H, 6·0; N, 4·1; Br, 24·1. $C_{27}H_{33}O_4N_2Br,HBr,2H_2O$ requires C, 50·3; H, 5·9; N, 4·3; Br, 24·8%), $\lambda_{max.}$ (in water) 242·5 (log ε 4·5), 305 (log ε 4·25), and 452 mμ (log ε 4·25). 1-(3 : 4-Dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)-2-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolylmethyl)pentane dihydrobromide [30] had $\lambda_{max.}$ 242·5 (log ε 4·43), 305 (log ε 4·2), and 452 mμ (log ε 4·15).

(±)-*De-ethylemetine Dihydriodide* (XV).—*Racemate A*. The iodide hydriodide (XIV) (3·52 g.) was hydrogenated in methanol (150 c.c.) with Adams catalyst (0·2 g.) at room temperature and pressure. Absorption was slow but after 24 hr. the theoretical amount of hydrogen had been taken up and reduction ceased. The pale yellow solution was filtered and concentrated, prisms (1·5 g., 42%), m. p. 236—240° (softening at 234°), separating. Crystallisation from methanol gave the *dihydriodide A*, m. p. 247—249° (softening at 243°) (Found: C, 45·6, 45·2; H, 5·5, 5·6; N, 4·0, 3·3; I, 35·8. $C_{27}H_{36}O_4N_2,2HI$ requires C, 45·8; H, 5·4; N, 4·0; I, 35·8%). The base did not crystallise. Ethereal hydrobromic acid gave the *dihydrobromide*, m. p. 218—220° (from ethanol–ethyl acetate) (m. p. less sharp than for the dihydriodide, possibly owing to hydration) (Found: C, 48·4; H, 6·7; N, 3·8. $C_{27}H_{36}O_4N_2,2HBr,3H_2O$ requires C, 48·5; H, 6·6; N, 4·2%), $\lambda_{max.}$ (in water) 227 (log ε 4·17) and 282 mμ (log ε 3·85). The *dihydrogen dioxalate*, prepared from the dihydrobromide in the normal way, formed prisms (from methanol–ether) which softened at 120° and had m. p. 123—125° (meniscus at 140°) (Found: C, 56·0; H, 6·3; N, 4·3. $C_{27}H_{36}O_4N_2,2H_2C_2O_4,2H_2O$ requires C, 55·6; H, 6·6; N, 4·2%).

Racemate B. After separation of the dihydriodide A no further material could be obtained crystalline. However, evaporation gave a non-hygroscopic yellowish, amorphous powder, m. p. 210—220° (softening at 205°) (Found: C, 44·2; H, 5·7; N, 3·6%).

In a similar experiment, this product was dissolved in water, and the solution was made alkaline and extracted with chloroform. The base was treated with ethanolic oxalic acid. Ether was added. The precipitated oil crystallised slowly (1·06 g., 33%); on crystallisation from methanol–ethyl acetate, the *salt B* separated very slowly as prisms, m. p. 180° (decomp.) (Found: C, 59·4; H, 6·7; N, 4·5%). A mixed m. p. with the racemate A dihydrogen dioxalate was 112—140°.

In another experiment the amorphous dihydriodide (1·31 g.) was dissolved in methanol with warming; from the cooled solution ethereal hydrobromic acid precipitated a yellow gum. Crystallisation from methanol–ethyl acetate gave pale yellow prisms (0·31 g.), m. p. 225—230°. Recrystallisation gave prisms, soften at 218°, m. p. 224—228° (mixed m. p. with the dihydrobromide of racemate A, 212—227° (Found: C, 50·0; H, 6·7; N, 4·1; Br, 24·1. $C_{27}H_{36}O_4N_2,2HBr,2H_2O$ requires C, 49·8; H, 6·5; N, 4·3; Br, 24·6%), $\lambda_{max.}$ (in water) 228 (log ε 3·91) and 282 mμ (log ε 3·55).

De-ethylrubremetinium Bromide (XIII) (cf. ref. 23).—The amorphous racemates of de-ethylemetine dihydriodide, after removal of the crystalline racemate A—1·5 g. obtained from the mother-liquor by evaporation to dryness—were heated with potassium acetate (0·25 g.), mercuric acetate (5 g.) and acetic acid (1 c.c.) in water (32 c.c.) for 1 hr., then filtered. The mercurous acetate was washed with water, alcohol, and acetone. The washings were added to the first filtrate and the alcohol and acetone were removed under reduced pressure. A further quantity of mercuric acetate (2·5 g.) was added and the solution refluxed again for 2 hr. The solution was filtered and the mercurous acetate washed with water. The filtrate was heated to 90° and hydrogen sulphide was passed into the solution. Mercuric sulphide was filtered off and extracted exhaustively with boiling ethanol. The total filtrates were concentrated under reduced pressure to *ca.* 30 c.c. and treated with excess of 48% aqueous hydrobromic acid. The

[30] Osbond, *J.*, 1952, 4785.

orange-scarlet needles (0·80 g., 72%), m. p. 237—240° (soften at 230°), which separated, were collected. Recrystallisation from dilute hydrobromic acid gave *de-ethylrubremetinium bromide*, m. p. 233—235° (Found: C, 57·8; H, 5·9; N, 4·8. $C_{27}H_{29}O_4N_2Br,2H_2O$ requires C, 57·7; H, 5·9; N, 5·2%).

This oxidation product was also obtained by Pailer and Strohmayer [13b] but no experimental details or analyses are given; they record m. p. 215°.

Our product had $\lambda_{max.}$ (in H_2O) 257·5 (log ε 4·28), shoulder 283 (log ε 4·24), 300 (log ε 4·26), and 437·5 mμ (log ε 4·47). The absorption curve is identical with that given by Pailer and Strohmayer for this compound and with that for rubremetinium bromide.[24]

We thank Dr. Schnitzer and his associates (Hoffmann-La Roche Inc., Nutley) for the biological results, Dr. A. Cohen for his interest, and Mr. M. Tadd for assistance.

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433. *Structural Investigations on the Water-soluble Polysaccharides from the Green Seaweed* Acrosiphonia centralis (Spongomorpha arcta).

By J. J. O'Donnell and Elizabeth Percival.

Water-soluble sulphated polysaccharides containing D-glucose, D-xylose, L-rhamnose, and D-glucuronic acid, together with small amounts of D-galactose and D-mannose, have been extracted from *Acrosiphonia centralis*. Chloroform-extraction of the acetylated material separates *ca.* 9% of a glucose-rich fraction resembling starch. Further study of the main polysaccharide material revealed the presence of end-group xylose, 1 : 4-linked xylose and rhamnose, and a relatively large proportion of triply linked rhamnose. Sulphate groups are attached to rhamnose and/or xylose residues. All the uronic acid residues appear to be present as end-groups linked to rhamnose. 4-*O*-β-D-Glucopyruronosyl-L-rhamnose was separated and characterised. This polysaccharide is compared with the water-soluble polysaccharides of *Cladophora rupestris* and of *Ulva lactuca*.

In view of the close botanical relation between the green seaweeds, *Cladophora rupestris* and *Acrosiphonia centralis* (*Spongomorpha arcta*), and of the studies on the water-soluble polysaccharide of the former,[1] it seemed desirable to determine whether *A. centralis* synthesised similar material. Collection of pure species of the latter weed is difficult, and we are grateful to Dr. R. Lewin who sent us from Nova Scotia sufficient material for a preliminary investigation. It was at once apparent that the two water-soluble extracts were different and that large-scale investigations of *A. centralis* were warranted. Mr. H. Powell very kindly collected pure species of this weed from a single area at Millport, and the structural investigations now reported have been carried out on the water-soluble polysaccharides isolated from this material.

After removal of free sugars and most of the colouring matter by extraction with aqueous ethanol, water-soluble polysaccharide material was separated (mainly as the ammonium salt) from the residual weed by extraction with aqueous ammonium oxalate. Relatively little glucose remained in the weed after this extraction and it follows therefore that the cellulose content of *A. centralis* must be very small.

In Table 1 the properties of the water-soluble extract and the molar proportions of the sugars present in a partial hydrolysate are compared with those for similar extracts from *Cladophora rupestris* [1] and from *Ulva lactuca*.[2] The neutral sugars in the partial hydrolysate from *A. centralis* were separated and characterised as crystalline sugars or their derivatives. Hydrolysis for longer periods or with more concentrated acid led to extensive degradation.

[1] Fisher and Percival, *J.*, 1957, 2666.
[2] Brading, Georg-Plant, and Hardy, *J.*, 1954, 319.

The sulphate content (3·8%) calculated from the sulphated ash comprises half the total sulphate (7·8%), providing evidence of sulphate esters in the polysaccharide.

The water-soluble polysaccharide material from *C. rupestris* (see Table 1) has a positive

TABLE 1.

Molar proportions	*Cladophora rupestris* [1]	*Acrosiphonia centralis*	*Ulva lactuca* [2]
Arabinose	3·7	—	—
Galactose	2·8	0·1	—
Xylose	1·0	1·6	1·3
Rhamnose	0·4	1·4	4·4
Glucose	0·2	1·0	1·0
Mannose	—	0·2	—
Uronic acid (%)	3·0	19·3	20·8
SO_4^{2-} (%)	16·1	7·8	17·5
Ash (%)	13·7	10·0	19·0
$[\alpha]_D$ (in H_2O)	+69°	−31°	−47°

rotation and consists mainly of arabinose, galactose, and xylose units: the polysaccharides from the two other green seaweeds have negative rotations and comprise mainly glucose, xylose, rhamnose, and uronic acid residues. Although all three extracts contain ester sulphate groups it is plain that the extract from *A. centralis* more nearly resembles that from *U. lactuca*. The difference in the relative proportions of the sugars in the two extracts containing much uronic acid may be due, at least in part, to the resistance of polyuronides to hydrolysis; the *A. centralis* hydrolysate comprises *ca.* 45% of oligouronic acids containing uronic acid and sugar residues.

The sulphate (7·8%) and uronic anhydride (20%) in *A. centralis* extract correspond to about one residue to every eight and four sugar units respectively. A hydrolysate with 20% of uronic acid, present as unhydrolysed barium uronosylaldose, would contain *ca.* 16% of aldose and 6% of barium; *i.e.*, 40—45% of the neutralised hydrolysate would consist of barium uronates, which is in agreement with the experimental findings.

The free-acid polysaccharide has an equivalent weight of 459. In the absence of sulphate and ash, a 20% uronic acid content corresponds to an equivalent weight of 870. A sulphate content of 7·8% represents 67 g. (0·70 equivalent) of sulphate in 870 g. Hence 870 g. correspond, not to 1, but to 1·70 equivalents, and the calculated equivalent weight of a polysaccharide containing 20% of uronic acid and 7·8% of sulphate is 870/1·70, *i.e.*, 512. The uronic acid and sulphate content were determined on neutral polysaccharide which contained 10% of ash; it is permissible therefore to deduct 10% in the above calculation of the theoretical equivalent weight. The final calculated value then becomes 461, in excellent agreement with the experimental value.

The periodate consumption by the polysaccharide corresponds to *ca.* 1 mole, and the formic acid release to *ca.* 0·6 mole, for every anhydro-sugar residue. These results indicate that many of the units have free contiguous hydroxyl groups. An oxopolysaccharide was isolated, after dialysis, in 68% yield, and hydrolysis showed that this contained intact xylose and rhamnose units. There is, therefore, an indication of the presence of either 1 : 3-linked units or of branch points in the molecule.

Attempted fractionation of the free polysaccharide was unsuccessful. Acetylation, followed by chloroform-extraction, gave, however, a glucose-rich acetate (A) (9%), $[\alpha]_D$ +71° (devoid of sulphate). The deacetylated material resembled starch in its reactions with iodine. Methylation of this acetate (A) and hydrolysis of the product, followed by separation and characterisation of the methylated sugars, confirmed this structure, and also indicated some branching at position 6 of the sugar units. 2 : 3 : 4 : 6-Tetra- (1 part), 2 : 3 : 6-tri- (4 parts), and 2 : 3-di-*O*-methylglucose (1 part) were separated and identified. 2 : 3 : 6-Tri-*O*-methylmannose (*ca.* 10%) was also separated from this hydrolysate, proving the presence of 1 : 4-linked mannose residues, and suggesting the presence of a small quantity of a mannan or glucomannan. The presence of small amounts of 2 : 3 : 4-tri- and

2 : 3-di-*O*-methylxylose and of methylated acids is considered to be due to incomplete separation of the main polysaccharide material.

After removal of the glucose-rich fraction from the acetylated *A. centralis* extract the residual material (B), $[\alpha]_D$ −38°, was methylated and the product (OMe, 35·6%) hydrolysed. 2 : 3 : 4-Tri-*O*-methylxylose (1 part), 2 : 3-di-*O*-methylxylose (3 parts), 2 : 3-di-*O*-methylrhamnose (3 parts), and 2-*O*-methylrhamnose (5 parts), together with small quantities of 2 : 3 : 6-tri- and 2 : 3-di-*O*-methylglucose, were separated and characterised. Since both the methylated glucoses separated from this fraction were also present in the hydrolysate of the methylated fraction (A), their presence in both fractions is probably due to incomplete separation of the glucan from the polysaccharide(s) acetate.

These observations reveal structural similarities between the polysaccharides of the two weeds, *Ulva* and *Acrosiphonia*. Both polysaccharides carry xylose end groups and have 1 : 4-linked xylose and rhamnose. The isolation of a monomethylrhamnose, in relatively large quantity, from the methylated *Acrosiphonia* extract, is evidence that rhamnose occurs at branch points in the molecule.

In spite of the use of a wide variety of hydrolytic conditions no-one, so far as the authors are aware, has yet succeeded in isolating glucuronic acid or its lactone from any of the green seaweeds, the conditions required for complete hydrolysis invariably leading to degradation. Fractionation of the acidic material from the partial hydrolysate of the extract from *A. centralis* led to the separation of di- (10%), tri- (4%), and tetra-oligouronic acids (3%). A large polymeric fraction (65%) was also isolated, prolonged acid hydrolysis of which afforded the original mixture of oligouronic acids. Glycosidation, reduction, and hydrolysis of the first three fractions gave syrups consisting of varying proportions of glucose and rhamnose. The syrup from the first fraction had $[\alpha]_D$ −6° and was shown by quantitative chromatography [3] to contain equimolar proportions of D-glucose and L-rhamnose, the former being characterised by oxidation by the specific enzyme,[4] glucose oxidase, and the latter by formation of the authentic crystalline benzoylhydrazone. It is considered therefore that the glucose arose from the reduction of glucuronic acid residues. The ester glycoside of this fraction consumed 2·8 moles of periodate per mole, indicating that linkage occurred through position 2 or 4 of the rhamnose residue; methyl 2- or 4-glucuronosylrhamnoside requires 3 mols. of periodate for complete oxidation, whereas methyl 3-glucuronosylrhamnoside reduces only 2 mols. Methylation of the reduced ester glucoside confirmed these findings. Crystalline 2 : 3 : 4 : 6-tetra-*O*-methylglucose and syrupy 2 : 3-di-*O*-methylrhamnose were separated from the hydrolysate of the methylated disaccharide. The tetra-*O*-methylglucose could only have arisen from glycosidically linked glucuronic acid, and the biuronic acid has therefore the constitution 4-*O*-β-D-glucopyruronosyl-L-rhamnose, the β-configuration being inferred from the negative specific rotation. The chromatographic mobility ($R_{glucose}$ *ca.* 1·0) of this fraction is high for an aldobiuronic acid (cf. 2-*O*-D-glucuronosyl-L-rhamnose, $R_{glucose}$ 0·24) and it seemed likely that, in the free state, it existed as the lactone. Chromatographic support for this conclusion was obtained, inasmuch as it behaved in the same way as glucurone on similar treatment. Both migrated back from the starting line on ionophoresis at pH 5·5, indicating the absence of charged groups at this pH, whereas at pH 10 their respective M_G values are 0·75 and 0·96; in addition they each gave two spots if treated with ammonia before development. In this connection it is worth noting that the equivalent weight (328) of this fraction is closer to the calculated value (322) for the lactone of glucuronosylrhamnose than to the calculated value for the free biuronic acid (340).

The trisaccharide had equivalent weight 249 and molecular weight 508: a diglucuronosyl-*O*-rhamnose would require 257 and 514 respectively. In agreement with this structure, glycosidation, reduction, and hydrolysis afforded glucose and rhamnose in the molar proportions of *ca.* 2 : 1.

[3] Pridham, *Analyt. Chem.*, 1956, **28**, 1967.
[4] Keilin and Hartree, *Biochem. J.*, 1948, **42**, 230.

The tetrasaccharide fraction was difficult to purify and, although equimolar proportions of glucose and rhamnose were obtained on hydrolysis of the reduced material, the values for the equivalent and molecular weights cannot be explained on this basis and further evidence must be awaited.

Reduction and hydrolysis of the glycoside ester of the acidic polymeric fraction afforded equimolar proportions of glucose and rhamnose, together with a very small amount of xylose. The low yield (24%) from this reaction is attributable to the low solubility of the material in the organic solvents employed for reduction.

Methylation studies of the acidic material confirmed these results. After removal of the neutral methylated sugars the methylated oligouronic acids were separated on thick paper. After glycosidation, reduction, and hydrolysis, the first fraction gave equimolar proportions of 2 : 3 : 4-tri-*O*-methyl-D-glucose and 2-*O*-methyl-L-rhamnose. This fraction therefore consisted of 2 : 3 : 4-tri-*O*-methyl-4-*O*-D-glucopyruronosyl-2-*O*-methyl-L-rhamnose and almost certainly originated from the same portion of the molecule as the 4-*O*-D-glucopyruronosyl-L-rhamnose, isolated from the hydrolysate of the unmethylated extract. Furthermore it follows that these units must be linked to the rest of the molecule through the hydroxyl group on position 3 of the rhamnose. Each of the remaining acidic fractions was similarly treated and each gave rise to approximately equimolar proportions of 2 : 3 : 4-tri-*O*-methylglucose and a non-reducing syrup with a high chromatographic mobility (R_G 1·15). The latter material did not reduce periodate and gave a positive test for methoxyl. These properties are in agreement with the structure, 1 : 4-anhydro-2-*O*-methylrhamnitol. Although it has been shown that rhamnitol, on treatment with acid, gives the 1 : 4-anhydro-derivative [5] it is difficult to see how this product could have arisen from the methylated acid fraction. Only if cleavage of the glycosidic links occurred before or during the reduction would rhamnitol be produced. Although comparison with reduced 2-*O*-methylrhamnose suggests that this non-reducing syrup derived from the acid fraction probably arose from rhamnose residues in the polysaccharide its characterisation as 1 : 4-anhydro-2-*O*-methylrhamnitol can only be regarded as tentative.

Methylation failed to reduce the proportion of sulphate groups in the polysaccharide (B). The allocation of these groups to individual sugar residues is a difficult problem; their attachment to glucose residues is very unlikely in view of the separation of a sulphate-free glucan and of the small amount of glucose in polysaccharide (B). The reduced glucuronic acid residues were isolated solely as 2 : 3 : 4-tri-*O*-methylglucose and must therefore occur as glycosidically linked end-groups with all the hydroxyl groups free for methylation. This leaves only xylose and/or rhamnose for union with the sulphate groups. 2 : 3-Di-*O*-methylxylose and 2 : 3-di-*O*-methylrhamnose were isolated in approximately equal quantities together with about twice as much mono-*O*-methylrhamnose. There are barely enough xylose residues to accommodate all the sulphate groups. Furthermore, if sulphate is linked to position 4 of those xylose units isolated as 2 : 3-di-*O*-methylxylose then practically all the xylose residues in the molecule are present as end-groups, many of which are sulphated. A likely site, therefore, for some at least of the sulphate groups, is on the rhamnose residues.

The polysaccharide(s) (B) must have a highly complicated structure. At least part of the molecule consists of 1 : 3-linked rhamnose residues carrying glucuronic acid units linked at position 4. The results of methylation studies have revealed the presence of the following residues:

GA...	...4 R 1...	...4 R 1... 3 ⋮	...4 X 1...	X 1...	...4 G 1...	...4 G 1... 6 ⋮
(25%)	(11%)	(21%)	(11%)	(4·2%)	(1·7%)	(0·6%)

GA = glucuronic acid, G = glucose, R = rhamnose, X = xylose.

[5] G. Buchanan, personal communication.

The rest of the material (*ca.* 24%) comprises the non-reducing material isolated from the acid fraction.

Experimental

Analytical Methods.—All solutions were evaporated under reduced pressure below 60°. Paper partition chromatography was carried out on Whatman No. 1 paper with upper layers of the following solvent systems (v/v) (1) butan-1-ol–benzene–pyridine–water (5 : 1 : 3 : 3); (2) ethyl acetate–pyridine–water (10 : 4 : 3); (3) ethyl acete–acetic acid–formic acid–water (18 : 4 : 1 : 5); (4) ethyl acetate–acetic acid–water (3 : 1 : 3); (5) butan-1-ol–acetic acid–water (4 : 1 : 5); (6) butan-1-ol–ethanol–water (4 : 1 : 5); (7) ethyl methyl ketone half saturated with water plus ammonia (99 : 1); (8) ethyl acetate–acetic acid–water (9 : 2 : 2). Papers were sprayed with a saturated aqueous solution of aniline oxalate. R_G, R_{Gl}, G_{GA}, and R_F are the rates of travel relative to tetramethylglucose, glucose, glucuronic acid (glucurone co-spotted with ammonia), and the solvent front respectively. Ionophoresis [6] was carried out (750 v; 12·5 mA) in borate buffer at pH 10, and the ionophoretograms were sprayed with saturated aqueous aniline oxalate containing 20% of acetic acid. Specific rotations were measured for solutions in water at 18°.

Acrosiphonia centralis (100 g. dry), collected from Millport in April and June 1957, was thoroughly washed with sea-water, dried in a current of air at room temperature, and extracted under reflux with 85% aqueous ethanol until the alcoholic extracts were colourless. The residual weed was then exhaustively extracted at 95° with 1% ammonium oxalate solution and with water, and at room temperature with 0·01N-hydrochloric acid, 2% aqueous sodium carbonate, and 5% aqueous potassium hydroxide. The extracts were each dialysed until free from inorganic material, and the polysaccharides isolated by freeze-drying. Chromatography [3] of the hydrolysate of each extract revealed that they all contained the same sugar residues, and in approximately the same proportions. The weed remaining after extraction with ammonium oxalate was kept for 10 days in 72% sulphuric acid solution.[7] The filtered solution was diluted with water to a strength of N, then heated at 100° for 7 hr. The resulting syrup contained glucose : xylose : rhamnose (1 : 1 : 1) together with minute quantities of oligouronic acids (paper chromatography, visual examination).

Extraction with ammoniun oxalate gave the highest yield (12% of the dry weight of weed) of water-soluble polysaccharide, and a comparison of the properties of this extract with those of the hot water extract (4·5% yield) demonstrated the essential similarity of the two materials:

Extract	Ash (%)	Sulphate (%)	Nitrogen (%)
Hot water	13·9	7·8	1·0
Ammonium oxalate	10·0	7·8	4·2

In view of these findings all the subsequent investigations were carried out on an ammonium oxalate extract.

The polysaccharide (12 g.) was isolated, as an off-white powder, by freeze-drying. It had $[\alpha]_D$ −31° (*c* 1·2) [Found: N (as ammonium salt by direct distillation with alkali) 3·6, (Kjeldahl) 4·2; ash (direct) 10·0; (as sulphate) 11·8; SO_4^{2-} in ash 32; total SO_4^{2-}, 7·8; uronic anhydride,[8] 20·3%].

Attempted Fractionation of the Aqueous Extract.—10% Aqueous cetyltrimethylammonium bromide (5 c.c.) was added dropwise, with stirring, to an aqueous solution of the extract (189 mg. in 20 c.c.). Regeneration [9] of the polysaccharide from the complex and from the supernatant liquid gave 132 mg. (SO_4^{2-}, 8·1%) and 37 mg. (SO_4^{2-}, 9·5%) respectively. Four successive fractionations in all were carried out; in each case hydrolysates of material both from the complexes and the supernatant layers revealed the presence of glucose, xylose, and rhamnose with no significant difference in their relative proportions (paper chromatography).

Treatment of the extract with aqueous solutions of copper sulphate and copper acetate failed to achieve fractionation.[10]

Equivalent-weight Determination.—An aqueous solution of the polysaccharide (133 mg. in

[6] Foster, *Chem. and Ind.*, 1952, 1050.
[7] Monier-Williams, *J.*, 1921, **119**, 803.
[8] Swenson, McCready, and Maclay, *Ind. Eng. Chem. Anal.*, 1946, **18**, 290.
[9] Bera, Foster, and Stacey, *J.*, 1955, 3788.
[10] Hough, Jones, and Wadman, *J.*, 1952, 3393.

20 c.c.) was recycled four times through a column of Amberlite IR-120H resin (10 g.), and the eluant freeze-dried to a white powder (Found: ash, nil; SO_4^{2-}, 7·5%). The equivalent weight of this material, determined by titration with 0·01N-sodium hydroxide, was 459 (mean of several determinations).

Hydrolysis of the Polysaccharide.—(*a*) The polysaccharide (0·335 g.) was hydrolysed with N-sulphuric acid (30 c.c.) at 100°. The course of the hydrolysis was followed by chromatography and measurement of specific rotation and reducing power (hypoiodite reduction [10]) on aliquot parts:

Time (hr.)	0	0·5	1	2	4	6	8
Iodine (0·01N; c.c.)	1·9	5·4	7·1	8·6	9·7	—	—
$[\alpha]_D$	−29°	−12°	−4°	+2°	+6°	+4°	+6°

Chromatography (solvent 1) revealed that glucose, xylose, and rhamnose were released within the first hour, accompanied by traces of neutral oligosaccharides; the oligosaccharides had entirely disappeared in 8 hr. The presence of uronic acids was indicated by a series of pink spots near the starting line. Traces of mannose and galactose were also visible.

(*b*) The polysaccharide (1 g.) was heated under reflux with 3% methanolic hydrogen chloride (25 c.c.) for 6 hr.; 15% methanolic hydrogen chloride (15 c.c.) was then added at 16-hourly intervals, four times in all (total hydrolysis time 70 hr.). Water (30 c.c.) was added and the mixture heated at 100° for 6 hr. Chromatography in solvent (3) failed to reveal the presence of glucuronic acid or its lactone.

(*c*) The polysaccharide (1 g.) was heated with 98% formic acid (50 c.c.) under reflux in nitrogen for 7 hr. The neutral sugars were separated by elution through a column of IR-45B resin (acetate form), and the column was washed with water until the eluant gave a negative Molisch reaction. The acid fraction was recovered by elution with N-formic acid. After repeated extraction with ether the aqueous-acid fraction was evaporated to dryness and exhaustively extracted with ethanol. Chromatography (solvent 3) of the concentrated ethanolic extracts revealed spots of R_{Gl} 1·05, M_G 0·75, and R_{Gl} 0·88 and 0·63 respectively (cf. glucurone R_{Gl} 2·4).

Partial Hydrolysis of the Polysaccharide and Separation of the Sugars.—The polysaccharide (3·25 g.) was hydrolysed with N-sulphuric acid for 7 hr. at 100°. After neutralisation of the cooled solution with barium carbonate, the hydrolysate (2·2 g.) was obtained as an amorphous solid. Quantitative analysis of the neutral sugars in this hydrolysate by a colorimetric method [3] gave the molar proportions of glucose (1·0), xylose (2·1), rhamnose (1·3); and by sodium periodate oxidation [11] glucose (1·0), galactose (0·12), mannose (0·21), xylose (2·2), and rhamnose (1·6). A portion of the hydrolysate (1·75 g.) was fractionated on a cellulose column (2·8 × 60 cm.) with butan-1-ol half saturated with water as eluant. R_F values are recorded for solvent (1).

Fraction 1. A yellow syrup (28·8 mg.), R_F 0·09, $[\alpha]_D$ −4° (*c* 2·29) (Found: OMe, nil), gave a positive Selivanoff test.

Fraction 2. Crystalline L-rhamnose hydrate (139 mg.), m. p. and mixed m. p. 68°, R_F 0·55; the derived benzoylhydrazone had m. p. and mixed m. p. 186°.

Fraction 3. A syrup (18·5 mg.), R_F 0·46, was chromatographically distinct from ribose and gave a positive Selivanoff test.

Fraction 4. Crystalline D-xylose (264 mg.), m. p. and mixed m. p. 145°, R_F 0·44, $[\alpha]_D$ +19° (*c* 1·0). The derived dibenzylidene dimethyl acetal had m. p. 186°.

Fraction 5. A syrup (39·0 mg.), R_F 0·38. Although contaminated with xylose it was mainly mannose (solvents 1 and 3); its identity was confirmed by isolation of mannose phenylhydrazone m. p. and mixed m. p. 188°.

Fraction 6. A syrup (56·6 mg.), R_F 0·33, $[\alpha]_D$ +53° (*c* 0·25); its identity as D-glucose was established by formation of the dichlorophenylhydrazone, m. p. and mixed m. p. 153°.

Fraction 7. A syrup (21 mg.), R_F 0·28, chromatographically identical with galactose (solvents 1 and 3). The derived diethyl mercaptal had m. p. and mixed m. p. with the diethyl mercaptal of D-galactose, 140—142°.

Fraction 8. Eluted with water, and isolated as an amorphous solid (820 mg.), R_F 0—0·07.

Examination of the acidic fraction. Fraction 8 (2·14 g., the combined products from two separations) was converted into the free acid (1·57 g.) by treatment with IR-120(H^+) resin and

[11] Hirst and Jones, *J.*, 1949, 1659.

an aqueous solution (10 c.c.), mixed to a slurry with cellulose powder, and freeze-dried. The product was applied to the top of a cellulose column (74 × 3·6 cm.) and eluted with solvent (8); R_{Gl} values recorded below are for solvent (3). Seven fractions were separated. Each of the fractions, after evaporation to small volume (10 c.c.), was treated with barium hydroxide (to remove traces of sulphuric acid) and filtered. The filtrate was exhaustively treated with ether in a continuous extractor to remove final traces of acetic acid. Deionisation with IR-120(H^+) resin afforded clear acidic syrups.

(*a*) Fraction 1 (0—2·5 l.) (144 mg.). Chromatography showed glucose, xylose, and rhamnose together with considerable streaking.

(*b*) Fraction 2 (2·5—3·6 l.). An aldobiuronic acid (227 mg.), $[\alpha]_D$ −6° (*c* 0·5), R_{Gl} 1·05, R_{GA} 0·85 (solvent 4); co-spotting with ammonium hydroxide before elution gave a second spot, R_{Gl} 0·57 (cf. D-glucurone R_{Gl} 2·4 and 1·0 under these conditions), M_G (in borate buffer pH 10) 0·75, (in acetate buffer pH 5·5) 0·0 (cf. glucose and glucurone which behaved similarly). Co-spotting with ammonia before ionophoresis in acetate buffer gave a second spot *ca.* 15 cm. from the starting line. Galacturonic acid in acetate buffer moves *ca.* 14 cm. in 5 hr. (Found: equiv., 328, by titration). The reducing power, compared with that of rhamnose monohydrate as standard, was measured by treatment with iodine in excess of sodium hydroxide solution. The mixture was set aside for 2 hr., then acidified with sulphuric acid and titrated with sodium thiosulphate. The aldobiouronic acid (12·4 mg.) had the reducing power of 6·55 mg. of rhamnose monohydrate. This corresponds to a molecular weight of 344. Hydrolysis of a portion with 2N-sulphuric acid gave only degradation products of the furfuraldehyde type (paper chromatography). A portion (204 mg. and 50 mg. from a previous fractionation) was heated under reflux with 2% methanolic hydrogen chloride for 6 hr. The resulting ester glycoside (266 mg.) was suspended in tetrahydrofuran (30 c.c.) which had been dried by distillation from sodium and from lithium aluminium hydride. A saturated suspension of the hydride in tetrahydrofuran (6 c.c.) was then added dropwise, and the solution refluxed for 1 hr. Dropwise addition of water (18 c.c.) was followed by filtration of precipitated aluminium hydroxide and treatment with IR-120(H^+) resin. After evaporation of the organic liquid the remaining aqueous solution (R) was diluted with distilled water to 50 c.c. To a portion of this (10 c.c.) an equal volume of 2N-sulphuric acid was added, and the mixture heated at 100° for 6 hr. Deionisation with IR-4B(OH^-) resin, evaporation to dryness, and methanol-extraction of the residue afforded a syrup (33·7 mg.). Chromatography (solvents 1 and 3), together with colorimetric estimation, revealed the presence of glucose and rhamnose in the molar proportion of 1 : 0·95. The hydrolysed material (30 mg.) was treated with glucose oxidase,[4] and the enzyme was later removed by addition of equivalent solutions of cadmium sulphate and barium hydroxide and filtration of the resulting precipitate. Evaporation followed by methanol-extraction yielded a syrup which contained only rhamnose (paper chromatography). The derived benzoylhydrazone had m. p. and mixed m. p. 185°.

A portion of the diluted solution (R) (4 c.c.) was deionised with IR-120(H^+) and IR-4B(OH^-) resin and evaporated to a clear glass (14·2 mg.) which was oxidised with 0·015M-sodium periodate (10 c.c.). The reduction of periodate after 44 hr. was found [12] to be equivalent to 2·8 moles of periodate per mole of disaccharide glycoside and proceeded only very slowly beyond this figure.

The remainder of solution (R) (containing 128 mg.) was methylated with 25% aqueous sodium hydroxide in nitrogen at 5°, and dimethyl sulphate (17 c.c.) was added dropwise with cooling and stirring during 6 hr. Next morning the mixture was remethylated twice more and then extracted with chloroform. Evaporation of the chloroform extracts afforded the reduced methylated disaccharide glycoside (98 mg.), $[\alpha]_D$ +7° (*c* 2·0 in methanol). Hydrolysis with aqueous-methanolic N-hydrogen chloride (1 : 1) gave a syrup (84 mg.) which was separated on 3MM paper (40 × 40 cm.) by elution with solvent (7). R_G values are recorded below for solvent (6).

Fraction (i). 2 : 3 : 4 : 6-Tetra-*O*-methylglucose (36 mg.), m. p. and mixed m. p. 94°, $[\alpha]_D$ 79° (*c* 0·9), R_G 1·0 (Found: OMe, 51·9. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%).

Fraction (ii). 2 : 3-Di-*O*-methylrhamnose (34 mg.), $[\alpha]_D$ +42° (*c* 2·9), R_G 0·86, M_G 0·02. Oxidation with periodate and chromatography of the product [13] revealed one spot, of R_F 0·81. Comparison with the oxidation product of authentic 2 : 4-di-*O*-methylrhamnose revealed spots of R_F 0·72, 0·78, and 0·85 (solvent 6). Cf. page 2177, fraction 2.

[12] Aspinall and Ferrier, *Chem. and Ind.*, 1957, 1216.
[13] Lemieux and Bauer, *Canad. J. Chem.*, 1953, **31**, 814.

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(*c*) Fraction 3 (3·6—4·4 l.) (58 mg.). Chromatography showed this to be a mixture of fractions 2 and 4.

(*d*) Fraction 4 (4·4—5·2 l.) (45 mg.), $[\alpha]_D$ +4° (*c* 0·5), R_{Gl} 0·88, R_{GA} 0·68 (solvent 8) (Found: equiv. 514, by titration; *M*, 508. Calc. for diglucuronosyl-*O*-rhamnose $C_{18}H_{28}O_{17}$: *M*, 516). Conversion into the ester glycoside and reduction, as for fraction 2, gave on hydrolysis a syrup consisting of glucose : rhamnose [3] 1·76 : 1.

(*e*) Fraction 5 (5·2—5·6 l.) (27 mg.) was a mixture of fractions 4 and 6.

(*f*) Fraction 6 (5·6—6·4 l.). The syrup (51 mg.), R_{Gl} 0·63, R_{GA} 0·44 (solvent 8) (Found: equiv. 690, by titration; *M*, 1050), on glycosidation, reduction, and hydrolysis, yielded a syrup containing glucose : rhamnose = 1 : 0·83.

(*g*) Fraction 7 (aqueous eluant) (974 mg.), R_{Gl} 0—0·4. Further hydrolysis (16 hr., 2N-HCl at 100°) of a portion of this syrup and chromatography of the hydrolysate revealed spots corresponding to the acidic oligosaccharides described above. Esterification, reduction, and hydrolysis afforded a syrup containing glucose : rhamnose = 1 : 0·88, together with a trace of xylose.

Periodate Oxidation of the Extract.—The extract (0·153 g.) in water (30 c.c.) was treated with 0·095M-sodium periodate (30 c.c.). The reduction of periodate and release of formic acid were measured on samples (1 c.c.) withdrawn at intervals: [1]

Time (hr.)	1·25	3·5	8	25	32	48	96
Moles of periodate reduced/anhydro-unit	0·47	0·61	0·70	0·90	0·98	1·08	1·20
Moles of formic acid released/ ,,	0·138	0·177	0·215	0·250	0·256	0·397	0·586

Oxidation was stopped after 96 hr. by passing sulphur dioxide through the cooled mixture. After dialysis, freeze-drying afforded the oxopolysaccharide (204 mg.) (Found: ash, 6·7; SO_4^{2-}, 8·6%). Chromatography of the hydrolysate (7 hr., N-H_2SO_4 at 100°)revea led the presence of small amounts of xylose and rhamnose.

Acetylation of the Polysaccharide.—The polysaccharide (13·8 g.), dispersed in formamide (100 c.c.) and pyridine (700 c.c.), was shaken with acetic anhydride (200 c.c.) during 72 hr. The mixture was added slowly with cooling to an equal volume of water. After dialysis and evaporation to small volume the polysaccharide (15·6 g.) was isolated by freeze-drying (Found: Ac 13·6%). Reacetylation gave an off-white powder (14·5 g.) (Found: Ac, 22·4%). Further treatment with acetic anhydride failed to increase the acetyl content. The acetylated material (12·7 g.) was exhaustively extracted with chloroform. Addition of light petroleum to the concentrated chloroform extracts afforded a white precipitate (polysaccharide acetate A; 0·91 g.). The chloroform-insoluble material (11·5 g.) will henceforth be called polysaccharide acetate (B).

Polysaccharide (*A*).—Polysaccharide acetate (A) had $[\alpha]_D$ +71° (*c* 1·2 in $CHCl_3$) (Found: SO_4^{2-}, nil). Deacetylation of a portion with sodium methoxide afforded a polysaccharide which gave a purple colour with iodine. This property was destroyed by prior treatment with α-amylase.[14] Hydrolysis of a portion and determination [3] of the molar proportions of the sugars present gave glucose : mannose : xylose = 1·0 : 0·31 : 0·17.

Deacetylation and methylation. The acetate (A) (0·82 g.), dissolved in ice-cooled 30% aqueous sodium hydroxide (20 c.c.), was treated dropwise with dimethyl sulphate (9 c.c.) with stirring in nitrogen during 6 hr. After being kept overnight the mixture was treated with a further quantity of sodium hydroxide and dimethyl sulphate as before.[15] The mixture was neutralised (pH 7) with sulphuric acid and dialysed until free from inorganic ions. Thallium hydroxide (2 g.) was added and the mixture freeze-dried. The resulting white powder was refluxed with methyl iodide (10 c.c.) until the solution was no longer alkaline (16 hr.).[16] After evaporation of the methyl iodide the residue was extracted at room temperature with methanol (3 × 25 c.c.), and with 50% aqueous methanol (3 × 25 c.c.); under reflux with 50% aqueous methanol (3 × 25 c.c.) and with water (3 × 25 c.c.). The combined extracts were methylated as before. After a third methylation and removal of the methyl iodide the residue was extracted with chloroform. Removal of the chloroform afforded a syrup (0·34 g.). Methylation with Purdie reagents twice gave a methylated product (0·324 g.) with $[\alpha]_D$ +42° (*c* 1·03 in $CHCl_3$) (Found: OMe, 38·6%). Hydrolysis with 4% methanolic hydrogen chloride (20 c.c.) under

[14] Rundle, Foster, and Baldwin, *J. Amer. Chem. Soc.*, 1944, **66**, 2116.
[15] Haworth, *J.*, 1915, **107**, 13.
[16] Fear and Menzies, *J.*, 1926, 937.

reflux for 3·5 hr. was followed by addition of N-hydrochloric acid (20 c.c.) and heating during a further 3·5 hr. The resulting syrup (0·28 g.) was fractionated on a cellulose column (1·9 × 45 cm.) with water-saturated light petroleum–butan-1-ol (7 : 3). R_G values are recorded below for solvent (6). The products of demethylation were identified by paper chromatography.[1]

Fraction 1 (1—71 c.c.). Syrupy 2 : 3 : 4 : 6-tetra-*O*-methylglucose (21 mg.), R_G 1·0, $[\alpha]_D$ +73° (*c* 0·24) (Found: OMe, 51·0. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%). Demethylation gave only glucose. The derived aniline derivative had m. p. and mixed m. p. 135°.

Fraction 2 (71—189 c.c.). A syrup (11·2 mg.) which revealed spots of R_G 1·0, 0·91, and 0·81, corresponding to 2 : 3 : 4 : 6-tetra- and 2 : 3 : 6-tri-*O*-methylglucose and 2 : 3 : 4-tri-*O*-methylxylose respectively, on chromatography. Demethylation gave glucose and xylose.

Fraction 3 (190—364 c.c.). A syrup (84 mg.), R_G 0·81, chromatographically identical with 2 : 3 : 6-tri-*O*-methylglucose in solvents (6) and (7), and having $[\alpha]_D$ +72° (*c* 0·78) (Found: OMe, 40·3. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). It gave only glucose on demethylation. An aliquot part (*c* 1·12) was kept at room temperature in 0·1N-methanolic hydrogen chloride and the change in rotation observed:

Time (hr.)	0·2	1	4	5	21	29	40	45	
$[\alpha]_D$.....	+0·74°	+0·52°	+0·26°	+0·24°	−0·19°	−0·25°	−0·32°	−0·32°	Final $[\alpha]_D$ −0·29°

Hydrolysis with 0·5N-hydrochloric acid gave the parent sugar. The derived lactone had $[\alpha]_D$ +33°.

Fraction 4 (379—469 c.c.). A syrup (16·5 mg.), R_G 0·76 (cf. 2 : 3-di-*O*-methylxylose, R_G 0·76; 2 : 4-di-*O*-methylxylose R_G 0·69), M_G 0·02, $[\alpha]_D$ +9° (*c* 0·7); it gave only xylose on demethylation.

Fraction 5 (470—553 c.c.) (19 mg.), R_G 0·76. Demethylation gave mannose and xylose.

Fraction 6 (554—1036 c.c.). A syrup (16 mg.), $[\alpha]_D$ +16° (*c* 0·8 in MeOH), R_G 0·76 identical with 2 : 3 : 6-, and distinct from 2 : 4 : 6- and 3 : 4 : 6-tri-*O*-methylmannose run as controls. It gave mannose on demethylation.

Fraction 7 (1037—1365 c.c.). A syrup (27 mg.), $[\alpha]_D$ +52° (*c* 0·9 in acetone) R_G 0·56 (Found: OMe, 29·2. Calc. for $C_8H_{16}O_6$: OMe, 29·6%), gave only glucose on demethylation and was chromatographically identical with 2 : 3-di-*O*-methylglucose run as a control (solvents 6 and 7). The derived aniline derivative had m. p. 133°, undepressed on admixture with specimen kindly given by Professor M. Stacey, F.R.S.

Fraction 8 (aqueous eluant). An amorphous solid (12·3 mg.), $[\alpha]_D$ −9° (*c* 0·3). Deionisation [IR-120(H^+) resin] gave an acidic syrup which revealed spots of R_P 0·70, 0·45, 0·40, 0·34, and 0·15 respectively (paper chromatography, solvent 5).

Polysaccharide (*B*).—The chloroform-insoluble acetate (B) had $[\alpha]_D$ +38° (*c* 1·15 in C_5H_5N) (Found: Ac, 22·0; SO_4^{2-}, 5·7%). Determination of the molar proportions [2] of the sugars present in a hydrolysate gave galactose : glucose : xylose : rhamnose = 0·06 : 0·56 : 1·69 : 1·31. Deacetylation and methylation of the residual material (11·3 g.) as for polysaccharide (A) gave a methylated product (5·3 g.), $[\alpha]_D$ −28° (*c* 1·3 in $CHCl_3$) (Found: OMe, 35·1; SO_4^{2-}, 5·4%). Further Purdie methylations failed to raise the methoxyl content. Fractionation of the methylated material (5·12 g.) by treatment with light petroleum (b. p. 60—80°) and addition of increasing quantities of chloroform gave the following fractions. Complete dissolution occurred in a mixture containing 40% chloroform (v/v):

Fraction	1	2	3	4	5	6	7	8
$CHCl_3$ in mixture (%)	0	5	10	15	20	25	30	40
Weight (mg.)	24	47	106	386	635	972	943	2060

A sample of each fraction was hydrolysed (N-H_2SO_4, 7 hr., 100°), and the hydrolysate examined by paper chromatography. Each of the hydrolysates contained methylated uronic acids (solvent 3) and exhibited no appreciable quantitative difference in the neutral methylated sugars present. The fractions were combined (5·1 g.) and hydrolysed as for the methylated polysaccharide (A) except that hydrolysis with aqueous acid was continued for 18 hr. The product (4·1 g.) was separated on a cellulose column (52 × 3 cm.) with water-saturated light petroleum–butan-1-ol (7 : 3); R_G values are recorded below for solvent (6).

Fraction 1. 2 : 3 : 4-Tri-*O*-methylxylose (87 mg.), R_G 0·95, $[\alpha]_D$ +22° (*c* 0·8) (Found: OMe, 48·0. Calc. for $C_8H_{16}O_5$: OMe, 48·1%). Demethylation afforded xylose. The aniline derivative had m. p. and mixed m. p. 97°.

Fraction 2. Crystallised slowly from methanol (230 mg.), this had m. p. 99°, R_G 0·88, M_G 0·0 (cf. 3 : 4-di-*O*-methylrhamnose M_G 0·36), $[\alpha]_D$ +42° (*c* 1·5) (Found: OMe, 32·4. Calc. for $C_8H_{16}O_5$: OMe, 32·3%). Demethylation gave rhamnose. The reduction of sodium periodate by this fraction and by 2 : 4-di-*O*-methylrhamnose was measured.[12] This was constant with both sugars after 20 hr. and corresponded to 1·6 and 0·9 mol. of periodate respectively. After addition of ethylene glycol the oxidation mixtures were examined by paper chromatography [13] (solvent 6). The product from fraction (2) gave one main spot, of R_G 0·81, whereas that from 2 : 4-di-*O*-methylrhamnose gave spots of R_G 0·72, 0·78, and 0·85 severally (aniline oxalate spray). *X*-Ray powder photographs of the crystalline sugar and of authentic 2 : 4-di-*O*-methylrhamnose were different.

Fraction 3. 2 : 3 : 6-Tri-*O*-methylglucose (35 mg.), m. p. and mixed m. p. 122°, R_G 0·81, $[\alpha]_D$ +70° (*c* 0·95) (Found: OMe, 42·0. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). Demethylation gave glucose.

Fraction 4. Syrupy 2 : 3-di-*O*-methylxylose (250 mg.), R_G 0·77 (cf. 2 : 4-di-*O*-methylxylose R_G 0·66), $[\alpha]_D$ +21° (*c* 3·0) (Found: OMe, 34·0. Calc. for $C_7H_{14}O_5$: OMe, 34·8%). Demethylation gave xylose. The aniline derivative had m. p. and mixed m. p. 145°.

Fraction 5. Syrupy 2-*O*-methylrhamnose (464 mg.), R_G 0·60, M_G 0·06 (cf. 3-*O*- and 4-*O*-methylrhamnose M_G 0·37 and 0·48 respectively), $[\alpha]_D$ +37° (*c* 3·5). The derived methylglycopyranoside reduced 1·1 moles of sodium metaperiodate per mole of glycoside. Paper chromatography of the oxidation products of the free sugar revealed a single spot of R_F 0·78. 4-*O*-Methylrhamnose on similar treatment gave a spot of R_F 0·95 (solvent 6). The aniline derivative had m. p. 146° undepressed on admixture with an authentic specimen of 2-*O*-methyl-*N*-phenylrhamnosylamine kindly supplied by Dr. L. Hough.

Fraction 6. Syrupy 2 : 3-di-*O*-methylglucose (14 mg.), R_G 0·52 (Found: OMe, 29·5. Calc. for $C_8H_{16}O_6$: OMe, 29·6%). Demethylation gave glucose. The aniline derivative had m. p. and mixed m. p. 132° [cf. polysaccharide (A), fraction 7].

Fraction 7. A syrup (26 mg.); R_G 0·30; in solvent (5), R_G 0·75.

Fraction 8, aqueous eluant. An amorphous solid (2·06 g.) which after treatment with IR-120(H^+) resin gave an acidic syrup (1·61 g.). Chromatography in solvent (5) gave spots of R_F 0·72, 0·53, 0·33, 0·25, 0·13, and 0·10; and R_G values of 0·87, 0·66, 0·41, 0·30, 0·16, and 0·12 respectively. Attempted separation on a cellulose column was unsuccessful, but was achieved on thick paper with this eluant: six fractions were collected.

The first (i), a syrup (161 mg.), R_G 0·87, $[\alpha]_D$ −12° (*c* 1·6), was converted into the ester glycoside and reduced with lithium aluminium hydride as for the aldobiuronic acid. This product was hydrolysed with N-hydrochloric acid at 100° for 4 hr. The resultant syrup (95 mg.) revealed two main spots, of R_G 0·84 and 0·61 respectively, together with a faint spot of R_G 1·15 (paper chromatography, solvent 6). Separation on thick paper (3MM) afforded: 2 : 3 : 4-tri-*O*-methylglucose (38 mg.) (characterised as below) and 2-*O*-methylrhamnose (36 mg.), R_G 0·61, $[\alpha]_D$ +34° (*c* 1·8), chromatographically and ionophoretically identical with fraction 5 separated from the hydrolysate of the neutral sugars from the methylated polysaccharide (B). After periodate oxidation this substance revealed a single spot, R_F 0·78 (solvent 6).

The other fractions (ii, 56 mg.; iii, 154 mg.; iv, 117 mg.; v, 360 mg.; and vi, 207 mg.) were each converted into their ester glycoside, reduced, and hydrolysed. Chromatography (solvent 6) of each hydrolysate revealed that fractions ii—v each gave two spots, of R_G 1·15 and 0·84. Fraction ii also gave a faint spot of R_G 0·61. Fraction vi gave the same spots as fractions ii—v and in addition spots of R_G 0·48, 0·33, 0·18, and 0·10 severally. Yields were as tabulated. Fractions ii—v were combined and separated into two further fractions (*a* and *b*) on thick paper.

Fraction	ii	iii	iv	v	vi
Weight (mg.)	56	154	117	360	207
Yield after reduction	31	92	68	204	82

(*a*) 2 : 3 : 4-Tri-*O*-methylglucose (142 mg. + 38 mg. from fraction i), R_G 0·84, $[\alpha]_D$ +53° (*c* 0·66) (Found: OMe, 41·2. Calc. for $C_9H_{18}O_6$: OMe, 41·9%), gave an infrared spectrum identical with that from 2 : 3 : 4-tri-*O*-methylglucose. The aniline derivative had m. p. 131°, not depressed on admixture with 2 : 3 : 4-tri-*O*-methyl-*N*-phenylglucosylamine, m. p. 139°.

(*b*) A yellow non-reducing syrup (113 mg.), R_G 1·15 (solvent 6), $[\alpha]_D$ +41° (*c* 2·0), was unattacked by periodate and gave a positive test for methoxyl. Comparison of the infrared spectra of this material with that of reduced (lithium aluminium hydride) 2-*O*-methylrhamnose

revealed that, while not identical in the finger-print region, the spectra indicated similarity in the molecular structure.

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[17] Hough, Powell, and Woods, *J.*, 1956, 4799.

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434. *The Chemistry of Quadrivalent Germanium. Part VI.*[1] *Ion-exchange Studies of More Concentrated Germanate Solutions.*

By D. A. EVEREST and J. C. HARRISON.

Ion-exchange studies of more concentrated germanate solutions have indicated the existence of a heptacondensed germanate ion $H_2Ge_7O_{16}^{2-}$. From experiments with resins of different water regain and with near-saturated germanate solutions it is postulated that the equilibrium monogermanate $\rightleftharpoons$ pentagermanate $\rightleftharpoons$ heptagermanate exists in germanate solutions. This equilibrium is displaced to the right on increasing the germanium concentration and to the left by increasing the pH above pH 9.

IN previous Parts [1-4] the condensation of germanic acid has been studied by ion-exchange techniques, whilst similar methods have been used for studying condensation reactions of boric,[5] arsenious,[6] telluric,[7] and vanadic acids.[8] With germanate solutions, pentagermanate ions $Ge_5O_{11}^{2-}$ were taken up by the resin at pH 9, whilst at higher pH values increasing quantities of monogermanate ions were sorbed by the exchanger owing to decondensation of the pentagermanate. Below pH 9 the amount of germanium sorbed by the resin decreased rapidly, although the R value of the sorbed species (*i.e.*, the average number of germanium atoms per " active site " of resin [2,6,8]) tended to remain near 2·5, the required value if the germanium was taken up as pentagermanate. Until recently the existence of pentagermanate in solution appeared to be confirmed both by the above experiments and by the results of other workers using a range of techniques.[9-13] However, Wittman and Nowotny [14] have shown that the solids previously considered to be pentagermanates [15,16] are actually derived from the heptacondensed acid $H_4Ge_7O_{16}$, the general formulæ of these compounds being $M_3HGe_7O_{16}$. Wittman and Nowotny consider that there is no evidence that the pentagermanate ion ever occurs in the solid state, and they also suggest that it is the $HGe_7O_{16}^{3-}$ ion which is the condensed germanate species occurring in the vicinity of pH 9 rather than the pentagermanate ion. Similar views have

[1] Part V, Everest and Harrison, *J.*, 1957, 4319.
[2] Everest and Salmon, *J.*, 1954, 2438.
[3] *Idem*, *J.*, 1955, 1444.
[4] Everest, *J.*, 1955, 4415.
[5] Everest and Popiel, *J.*, 1956, 3183.
[6] *Idem*, *J.*, 1957, 2433.
[7] *Idem*, *J. Inorg. Nuclear Chem.*, 1958, **6**, 153.
[8] Russell and Salmon, *J.*, 1958, 4708.
[9] Carpeni and Tchakarian, *Compt. rend.*, 1948, **226**, 725.
[10] Carpeni, *Bull. Soc. chim. France*, 1948, 629.
[11] Schwarz and Huf, *Z. anorg. Chem.*, 1931, **203**, 188.
[12] Souchay and Teyssedre, *Bull. Soc. chim. France*, 1951, 938; Bye, *ibid.*, 1953, 390; Souchay, *ibid.*, 1953, 395.
[13] Lourijsen-Teyssedre, *ibid.*, 1955, 1118.
[14] Wittman and Nowotny, *Monatsh.*, 1956, **87**, 654.
[15] Tchakarian and Carpeni, *Compt. rend.*, 1948, **226**, 1094.
[16] Tchakarian and Wallace, *Bull. Soc. chim. France*, 1954, 1067.

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been advanced by Edwards and his co-workers.[17] It is relevant that the compound previously considered to be crystalline pentagermanic acid [18] has been shown to be simply hydrated germanium dioxide.[19]

Re-examination of our ion-exchange data [1,3,4] indicates that R values obtained with germanate solutions up to *ca.* pH 9 are slightly, but significantly, above 2·5, increasing with increasing germanium concentration. As increasing its concentration usually increases the tendency for an acidic species to condense (*e.g.*, refs. 5, 6, and 7), it was considered that by increasing the germanium concentration it might be possible to detect the presence of more highly condensed species than pentagermanate by ion-exchange methods. Experiments have also been carried out on resins of different water regains in order to differentiate between germanate species with different degrees of condensation. This technique has been used by Russell and Salmon for studying the condensation of vanadic acid.[8]

Experimental

Solutions.—Weighed amounts of germanium dioxide were added to 75 ml. of boiled-out distilled water (40 ml. with the experiments with resins of different water regains), the resulting suspension boiled, and the minimum quantity of sodium hydroxide added very slowly to effect solution. After cooling, the pH was adjusted to the required value by addition of alkali. No chloride was present in the solutions used except that added as resin chloride. To prepare the solution containing 870 mg.-atoms of germanium per l., finely-ground germanium dioxide (10 g.) was added to 100 ml. of distilled water. The suspension was heated to 100° for 2—3 hr. with slow addition of 3N-sodium hydroxide (10 ml.), whereupon an optically clear solution was obtained. The pH of the resulting solution was 5·8.

Resins.—Amberlite I.R.A. 400 resin was used in most experiments; its water regain [20] in the chloride form was 0·82 g./g. of resin. The series of resins of different water regains were of the De-Acidite FF type. Their chloride capacities (in mequiv./g. of air-dried form) were respectively 3·91 for the resin of water regain (w.r.) 0·49, 3·12 for w.r. 0·60, 3·40 for w.r. 0·76, 2·85 for w.r. 0·91, 2·17 for w.r. 1·04, and 3·60 for w.r. 2·33.

Equilibrium Experiments.—Solutions were equilibrated with resin (0·25 or 0·5 g. of chloride form) for 14 days with frequent shaking. With resins of low water regain longer was allowed. In experiments with Amberlite I.R.A. 400 the germanium and chloride sorbed by the resin were eluted with 0·5N-sodium hydroxide (100 ml.), then 0·5N-sulphuric acid. Germanium and chloride were determined in aliquot parts of the combined eluate by iodometric [21] and gravimetric procedures respectively. In the experiments with the resins of different water regain the germanium and chloride on the resin at equilibrium were determined indirectly by analysis of the solution phase.

Results and Discussion

In Fig. 1 are shown R values for the germanate species sorbed on Amberlite I.R.A. 400(Cl) at pH 9 from solutions of different germanium concentrations. This pH was chosen as it is approximately that at which the maximum germanium sorption by the resin occurs.[1-4] The R values obtained increase with increasing germanium concentration, reaching a limiting value of 3·5 which can be accounted for by assuming that germanium is exclusively sorbed as the hepta-condensed species $H_2Ge_7O_{16}^{2-}$ from the more concentrated germanate solutions. This ion is similar to the hepta-condensed ion postulated by Wittman and Nowotny [14] and by Shaw *et al.*[17] The R values obtained previously at pH 9 from solutions containing 22·6 and 27·6 mg.-atoms of Ge/l., *i.e.*, 2·6 and 2·8 (interpolated values),[1,4] are in excellent agreement with the R values of 2·6 and 2·75 now obtained at corresponding germanium concentrations.

[17] Shaw, Corwin, and Edwards, *J. Amer. Chem. Soc.*, 1958, **80**, 1536.
[18] Carpeni, *J. Chim. phys.*, 1948, **45**, 130.
[19] Braur and Renner, *Z. anorg. Chem.*, 1955, **278**, 108.
[20] Pepper, Hale, and Reichenberg, *J.*, 1952, 3129.
[21] Everest, *J.*, 1953, 4117.

The results in Fig. 1 might be interpreted as indicating sorption of a mixture of hepta- and mono-germanate ions by the resin, the proportion of the germanium sorbed as hepta-germanate increasing with increasing germanium concentration in solution. This interpretation implies that no pentagermanate ions occur in germanate solution, and that all work indicating the pentagermanate ion [1-4, 9-13] was only a measure of an apparent penta-condensation resulting from a fortuitous ratio of mono- to hepta-germanic acids. It is significant that the concentrations of germanium in the solutions used in these previous investigations were all close to that necessary for the sorption of a germanate of overall R 2·5 by the resin at pH 9 (cf. Fig. 1). However, as discussed below, the above interpretation is not thought to be correct and it is considered that the R values of below 3·5 are due to

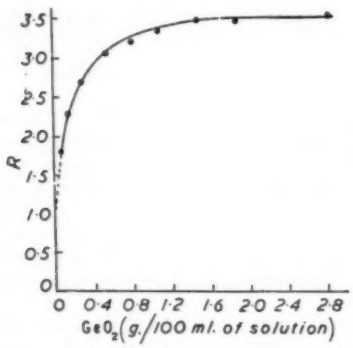

FIG. 1. *Variation of R with germanium concentration at* pH 9 *on Amberlite I.R.A.* 400 *resin.*

the sorption of a mixture of hepta-, penta-, and possibly mono-germanate ions by the resin.

In Fig. 2 are shown R values for the germanate species sorbed by resins of different water regains from a solution containing 132 mg.-atoms of germaniun per l. at pH 9. With resins of water regain 0·60 g./g. and above the R values all approach 3·5, indicating that heptagermanate is the chief germanate species present on these resins at equilibrium. The curve for the actual quantity of germanium sorbed by the 0·60 g./g. resin (Fig. 3) closely follows the R value curve for the resin germanate. It appears that in approaching equilibrium less highly condensed germanate species are initially sorbed by the resin and that these species are subsequently replaced by heptagermanate. All previous work indicates that the concentration of monogermanate is low in a germanate solution of pH 9, especially at the high germanium concentration used in these experiments; it is thus unlikely that monogermanate is the germanium species initially taken up by the exchanger.

With the resin of water regain 0·49 g./g., R remains close to 2·5, even after prolonged contact times, indicating that pentagermanate was the chief germanate species sorbed. With this resin the pore size is too small to allow take up of heptagermanate but it is sufficiently large to allow sorption of pentagermanate, *i.e.*, an ion-sieve effect occurs. This resin also differs in its behaviour from those of higher water regain in that the actual quantity of germanium sorbed by the exchanger slowly increases over a period of *ca.* 28 days whilst the R value of the resin germanate remains constant at 2·5 (Fig. 1). These results indicate both that the pentagermanate is only slowly taken up by the resin and also that no appreciable replacement of the species initially sorbed takes place as the system approaches equilibrium.

At equilibrium the 0·49 g./g. resin has only *ca.* 40% of its capacity occupied by sorbed germanium and only *ca.* 40% of the germanium initially present in solution is actually taken up by the resin. These two quantities are considerably greater in corresponding

experiments with more porous resins. This relatively low equilibrium uptake of germanium could be due to the presence of only a small concentration of pentagermanate in solution, although it would be expected that the selective sorption of pentagermanate by this resin would result in the solution equilibria's being displaced in favour of this ion with a resulting heavy uptake of pentagermanate by the resin. A more plausible explanation

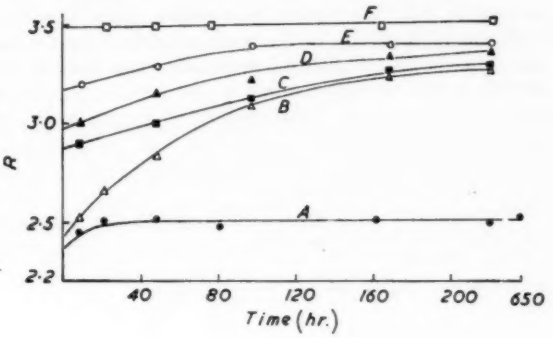

FIG. 2. *Variation of R with time using resins of different water regains. Germanium concentration in solution 132 mg.-atoms/l.*, pH 9.

Water regain of resins: *A* 0·49, *B* 0·60, *C* 0·76, *D* 0·91, *E* 1·04, *F* 2·53.

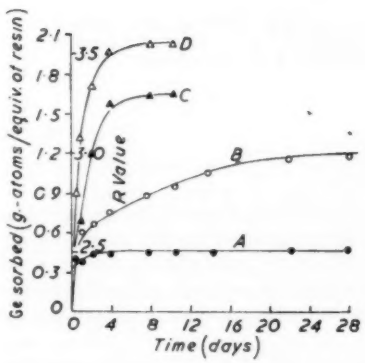

FIG. 3. *Variation with time of the R values and of the quantity of germanium sorbed by resins of water regain 0·49 and 0·60 g./g. Germanium concentration in solution 132 mg.-atoms/l.*, pH 9.

A, *R* values on 0·49 w.r. resin.
B, Ge sorbed on 0·49 w.r. resin, g.-atoms per equiv. of resin.
C, *R* value on 0·60 w.r. resin.
D, Ge sorbed on 0·60 w.r. resin, g.-atoms per equiv. of resin.

is that pentagermanate is itself partially excluded by the resin owing to variations in the pore size of the latter, this effect being enhanced by the fact that the hepta- and pentagermanate ions cannot differ greatly in size.

The 0·49 g./g. water regain resin was somewhat unstable to alkali. After two treatments with 2N-sodium hydroxide its water regain had risen to 0·55 and the resin was no longer excluding heptagermanate. It appears that when resins of known water regain are used as ion-sieves the water regain should be checked after each loading–elution cycle.

It is suggested from both present and previous results that the following equilibria exist in germanate solutions:

$$\text{Monogermanate} \rightleftharpoons \text{pentagermanate} \rightleftharpoons \text{heptagermanate}$$

these equilibria being shifted to the right by increasing the germanium concentration and to the left by increasing the pH above pH 9. The solutions investigated by Wittman and Nowotny [14] and by Shaw *et al.*[17] were relatively concentrated and would thus contain principally heptagermanate, but the more dilute solutions used by other workers would contain principally pentagermanate as the most highly condensed germanate species. It appears that in its condensations germanic acid shows many resemblances to boric [5] and telluric acids.[7]

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In Fig. 4 are shown R values for germanate sorbed on Amberlite I.R.A. 400 from solutions containing 178·1 mg.-atoms of Ge/l. between pH 5·8 and 10. With these solutions not only is the $H_2Ge_7O_{16}^{2-}$ ion the only germanate species sorbed by the resin below pH 9·7 but, more significantly, only little change occurs in the actual quantities of germanium and chloride sorbed by the resin (3·05 and 0·10 at pH 9·75 and 2·96 and 0·145 at pH 6·5, g.-atoms of Ge and Cl per equiv. of resin respectively). This exclusive sorption of heptagermanate and the constant germanium : chloride ratio on the resin is due to two factors. First, the high affinity of the heptagermanate ion for the resin (in absence of the ion-sieve effect) as compared with the resin affinity of the other ionic species present; this greater affinity of the heptagermanate is due to its high polarisability (the relation between the resin affinity and the polarisability of an ion is discussed elsewhere [22]). Secondly, the high ratio of germanium in solution both to the total chloride in the system and to the amount of germanium sorbed by the resin (0·25 g. of chloride-form resin equilibrated with 75 ml. of germanate solution).

Experiments were also carried out on the sorption of germanium by a high water-regain resin (2·3 g./g.) from the most concentrated germanium solution it was possible to

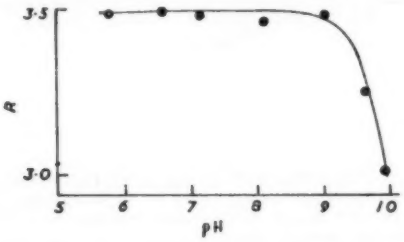

FIG. 4. *Variation of R with* pH *of solution on Amberlite* I.R.A. 400. *Germanium concentration* 178·1 *mg.-atoms/l.*

produce (870 mg.-atoms of Ge/l.). At pH 5·8 equilibrium between the resin and the solution phase was only slowly attained, R for the sorbed germanate being 2·8 after 24 hr., rising to 3·42 after 21 days. This slow attainment of equilibrium is probably due to the presence of only a small equilibrium concentration of heptagermanate in solution, a slow displacement of the solution equilibria taking place in favour of heptagermanate as this ion is removed by the resin from the solution phase.

At pH 8·1 equilibrium was rapidly attained, R reaching 3·5 after 24 hr. and remaining close to this value for 11 days. These results confirm that heptagermanate is the principal species present in concentrated germanate solutions at *ca.* pH 8—9. It was also found that after 21 days R had risen to 4·14. This result probably indicates that a more highly condensed species than heptagermanate occurs in trace quantities in concentrated germanate solutions, at least in the pH range 8—9.

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[*Received, January 28th,* 1959.]

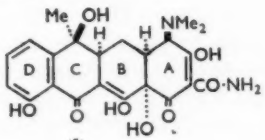
[22] Aveston, Everest, and Wells, *J.*, 1958, 231; Everest, Napier, and Wells, Conference for the Peaceful Uses of Atomic Energy, Geneva, 1958, paper A/Conf. 15/P/101.

435. *The Synthesis of Tetracyclines. Part I. Some Model Diene Reactions.*

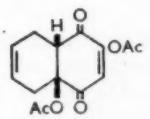
By J. A. Barltrop and M. L. Burstall.

Several naphthalene and anthracene derivatives containing angular acetoxy-groups have been prepared by reaction of butadiene and *cyclo*pentadiene with 2-acetoxy-1 : 4-quinones, and their structures have been determined by chemical degradation and comparison of their spectra with those of known compounds.

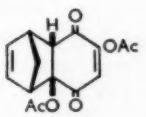
The tetracyclines are a group of powerful broad-spectrum antibiotics active [1] against both Gram-positive and Gram-negative bacteria and based [2] on the common structure (I). Our general synthetical study of this group began with an investigation of the stereochemically attractive [3] possibility of generating the *cis*-fused, angularly hydroxylated rings A and B by Diels–Alder reaction of a substituted diene with a 2-hydroxy-1 : 4-quinone. As only isolated examples of such reactions have been reported [4] we investigated first the reactions of simple dienes with 2 : 5-dihydroxybenzoquinone and 2-hydroxy-1 : 4-naphthaquinone and their derivatives.



(I)



(II)



(III)

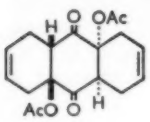
2 : 5-Dihydroxybenzoquinone, prepared by oxidising resorcinol with peracetic acid, decomposed on attempted reaction with butadiene, but its diacetate reacted smoothly in benzene at 120° to give *cis*-2 : 10-diacetoxy-1 : 4 : 5 : 8 : 9 : 10-hexahydro-1 : 4-dioxonaphthalene (II) in 69% yield. The structure of this compound was indicated by the resemblance of its ultraviolet absorption spectrum to that of the well-known [5] adduct of butadiene and 1 : 4-benzoquinone, and by its infrared spectrum, which showed the presence of ester carbonyl groups and a conjugated ketonic carbonyl group. This structure (II) was confirmed by conversion of the adduct into 2-hydroxy-1 : 4-naphthaquinone by aerial oxidation in hot alkaline solution. A similar 1 : 1 adduct (III) was formed by the reaction of 2 : 5-diacetoxybenzoquinone with *cyclo*pentadiene.

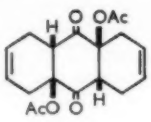
Prolonged reaction of butadiene with 2 : 5-diacetoxybenzoquinone or the adduct (II) gave almost quantitative yields of the *cis-cis*-11 : 13-diacetoxy-1 : 4 : 5 : 8 : 11 : 12 : 13 : 14-octahydroanthraquinone (IVa or b). The insolubility of this compound in ethanol prevented complete mapping of its ultraviolet absorption spectrum, but the absence of any definite maximum at wavelengths greater than 2200 Å supports the structure proposed (cf. the similar ultraviolet spectrum of 1 : 4 : 5 : 8 : 11 : 12 : 13 : 14-octahydroanthraquinone). Further, the infrared absorption spectrum showed the presence of a ketonic group in a saturated environment. Aerial oxidation of the adduct in alkaline solution gave anthraquinone. It is of interest that when this diene reaction was carried out under forcing conditions in an attempt to accelerate it the only crystalline product, obtained in only 14% yield, was an unstable yellow compound $C_{14}H_{12}O_2$. The resemblance of the physical properties of this compound to those of the unstable 5 : 8-dihydro-1 : 4-naphtha-

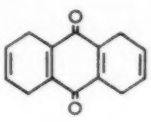
[1] Broschard, *Science*, 1949, **109**, 199; Finlay, *ibid.*, 1950, **111**, 85.
[2] Woodward, *et. al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 5455; Booth, "Antibiotics Annual," Proc. Symposium on Antibiotics, 1953, p. 46; Woodward, *et. al.*, *J. Amer. Chem. Soc.*, 1954, **76**, 3567.
[3] Alder and Stein, *Angew. Chem.*, 1937, **50**, 510.
[4] Butz and Butz, *J. Org. Chem.*, 1942, **7**, 198; 1943, **8**, 497; Fieser and Seligman, *Ber.*, 1935, **68**, 1748.
[5] Diels and Alder, *Ber.*, 1929, **62**, 2337.

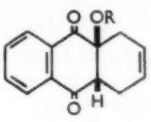
quinones [6] suggested that it is 1 : 4 : 5 : 8-tetrahydroanthraquinone (V); this view was confirmed by the presence in its infrared spectrum of a strong maximum at 6·10 μ (cf. 2 : 3 : 5 : 6-tetramethylbenzoquinone which absorbs [7] at 6·10 μ in Nujol) and by its oxidation to anthraquinone in alkaline solution.

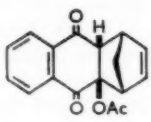
2-Hydroxy-1 : 4-naphthaquinone reacted sluggishly with butadiene in ethanol; the adduct (VI; R = H) could not be isolated but its formation was demonstrated by the isolation, in 35% yield, of anthraquinone on aerial oxidation of the reaction mixture in alkaline solution. 2-Methoxy-1 : 4-naphthaquinone similarly added butadiene with some difficulty. 2-Acetoxy-1 : 4-naphthaquinone, however, reacted smoothly with both butadiene and *cyclo*pentadiene to give the expected *cis*-fused acetates. The structure of the product (VI; R = Ac), formed in benzene at 100°, was shown by the resemblance of the ultraviolet absorption spectrum to that of 1 : 4 : 11 : 12-tetrahydroanthraquinone, by infrared bands showing the presence of ester and conjugated ketonic carbonyl groups, and


(IVa)


(IVb)


(V)


(VI)


(VII)

by aerial oxidation in alkaline solution to anthraquinone. However, in a reaction at 130° addition was accompanied by elimination, only 1 : 4-dihydroanthraquinone being isolated. A similar adduct (VII) was obtained by the reaction of 2-acetoxy-1 : 4-naphthaquinone with *cyclo*pentadiene. Both the adducts (VI; R = Ac) and (VII) were comparatively stable to heat and sublimed *in vacuo* without change.

The stereochemistry of the adducts described in this paper has been assigned on the known stereochemical selectivity of the Diels–Alder reaction as codified in the Alder–Stein rules.[3] The thermal stability of the adducts, which are derivatives of β-hydroxyketones, supports the postulated *cis*-ring-fusion since *trans*-dehydration at the ring junction is impossible. The instability of the adducts to alkali is explained on the assumption that the reagent, by catalysing a reversible enolisation, converts the adducts into *trans*-fused systems which can readily undergo an E_2 elimination.

Experimental

M. p.s are corrected. Ultraviolet absorption spectra were obtained with ethanol solutions. Infrared absorption spectra were determined for paraffin pastes.

2 : 5-*Dihydroxybenzoquinone* (with B. N. Chukwudebe).—Resorcinol (10 g.) in acetic acid (30 c.c.) was added slowly, with shaking and cooling, to 11% peracetic acid (200 c.c.). The dark red solution was kept overnight. The red-brown precipitate was collected, dried, and recrystallised from acetic acid, giving orange needles of 2 : 5-dihydroxybenzoquinone (8·7 g., 69%), m. p. 210—215° (decomp.) (Found: C, 51·7; H, 3·1. Calc. for $C_6H_4O_4$: C, 51·4; H, 2·9%). The diacetate was prepared by treating the quinone (5 g.) in acetic anhydride (15 c.c.) with 10% perchloric acid (0·5 c.c.). The mixture became yellow and heat was evolved. On cooling, lemon-yellow needles of 2 : 5-diacetoxybenzoquinone (5·2 g., 65%), m. p. 151—152°, separated (Found: C, 53·5; H, 3·6. Calc. for $C_{10}H_8O_6$: C, 53·6; H, 3·5%), $\lambda_{max.}$ 2600 Å (log ε 3·9), ν 5·65 (ester) and 6·0 μ (quinone).

cis-2 : 10-*Diacetoxy*-1 : 4 : 5 : 8 : 9 : 10-*hexahydro*-1 : 4-*dioxonaphthalene* (II).—2 : 5-Diacetoxybenzoquinone (25 g.), butadiene (10 c.c.), and benzene (50 c.c.) were heated in a sealed tube at 110° for 72 hr. The pale yellow solution obtained was evaporated to dryness, the residual gum was triturated with a little ether, and the buff solid formed was recrystallised from ether, yielding almost colourless rhombs of the *adduct* (II) (2·15 g., 69%), m. p. 120—121° (Found: C, 60·1; H, 5·2. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·0%), $\lambda_{max.}$ 240, 295 mμ (log ε 3·9, 3·05 respectively), ν 5·65, 5·75 (ester) and 5·9 μ (unsaturated ketone).

[6] Fieser, *J. Amer. Chem. Soc.*, 1948, **70**, 3165.
[7] Yates, Ardao, and Fieser, *J. Amer. Chem. Soc.*, 1956, **78**, 650.

For comparison, *cis*-1 : 4 : 5 : 8 : 9 : 10-hexahydro-1 : 4-dioxonaphthalene was prepared by the method of Diels and Alder;[5] it had $\lambda_{max.}$ 220, 270 mμ (log ε 4·1, 2·7 respectively), ν 5·95 μ.

Oxidation of the Adduct (II) *to* 2-*Hydroxy*-1 : 4-*naphthaquinone*.—The adduct (II) (1·5 g.), sodium ethoxide (1·8 g.) and methanol (10 c.c.) were heated under reflux for 4 hr., then cooled to 0°. The scarlet precipitate formed was collected, washed with a little cold methanol, dried, and dissolved in boiling water (15 c.c.). The filtered solution was acidified: the yellow precipitate was collected, dried, and sublimed *in vacuo*, yielding yellow needles of 2-hydroxy-1 : 4-naphthaquinone (0·39 g., 41%), m. p. 190—191° (decomp.) (Found: C, 68·6; H, 3·4. Calc. for $C_{10}H_6O_3$: C, 69·0; H, 3·5%). The infrared spectrum of the product was identical with that of authentic 2-hydroxy-1 : 4-naphthaquinone.

cis-2 : 10-*Diacetoxy*-1 : 4 : 5 : 8 : 9 : 10-*hexahydro*-5 : 8-endo*methylene*-1 : 4-*dioxonaphthalene* (III).—2 : 5-Diacetoxybenzoquinone (1·0 g.), freshly prepared *cyclo*pentadiene (2 c.c.), and benzene (30 c.c.) were heated in a sealed tube at 130° for 7 hr. The pale yellow solution was evaporated to dryness and the residue was triturated with ether until a solid formed. The latter, recrystallised from tetrahydrofuran, yielded the *adduct* (III) (0·89 g., 68%) as rhombs, m. p. 112—113° (Found: C, 62·0; H, 4·9. $C_{15}H_{14}O_6$ requires C, 62·1; H, 4·8%), ν 5·70, 5·80, and 5·95 μ.

cis : cis-11 : 13-*Diacetoxy*-1 : 4 : 5 : 8 : 11 : 12 : 13 : 14-*octahydroanthraquinone*.—The adduct (II) (0·5 g.), butadiene (5 c.c.), and benzene (25 c.c.) were heated in a sealed tube at 120° for 275 hr. The colourless solution obtained was evaporated to dryness and the residue was triturated with ether: a solid formed was recrystallised from ethyl acetate, yielding cis-cis-11 : 13-*diacetoxy*-1 : 4 : 5 : 8 : 11 : 12 : 13 : 14-*octahydroanthraquinone* (IV) (0·6 g., 100%) as rhombs, m. p. 211° (decomp.) (Found: C, 65·3; H, 6·1. $C_{18}H_{20}O_6$ requires C, 65·1; H, 6·0%), ν 5·75 and 5·8 μ. The ultraviolet spectrum showed no maximum beyond 2200 Å. The same product was formed by the reaction of 2 : 5-diacetoxybenzoquinone with butadiene under the same conditions.

cis : *cis*-1 : 4 : 5 : 8 : 11 : 12 : 13 : 14-Octahydroanthraquinone was prepared by the method of Diels and Alder.[5] Its ultraviolet spectrum showed no maximum beyond 2200 Å. Its infrared spectrum showed a maximum at 5·8 μ.

Oxidation of the Adduct (IV) *to Anthraquinone*.—The adduct (0·1 g.), potassium hydroxide (1·0 g.), and methanol (5 c.c.) were heated under reflux for 16 hr., then diluted with water (10 c.c.), and the pale yellow precipitate was collected, dried, and sublimed *in vacuo*, yielding anthraquinone (0·02 g., 32%), m. p. 285° (Found: C, 81·1; H, 4·1. Calc. for $C_{14}H_8O_2$: C, 80·7; H, 3·8%).

1 : 4 : 5 : 8-*Tetrahydroanthraquinone*.—The adduct (II) (0·5 g.), butadiene (3 c.c.), and benzene (10 c.c.) were heated at 170° for 40 hr. Cooling the almost colourless solution precipitated a yellow solid which recrystallised from ethanol, yielding 1 : 4 : 5 : 8-*tetrahydroanthraquinone* (V) (0·068 g., 14%) as yellow needles, m. p. 210—211° (decomp.), darkening rapidly in light (Found: C, 78·8; H, 5·6. $C_{14}H_{12}O_2$ requires C, 79·2; H, 5·7%), ν 6·10 μ. The mother-liquors, on treatment with hot alkali as in the previous experiment, gave anthraquinone (0·15 g., 33%), identified by means of its infrared spectrum.

The anthraquinone (V) (0·058 g.), potassium hydroxide (0·5 g.), and methanol (5 g.) were heated under reflux for 2 hr., then cooled. The precipitate was collected and worked up as before, yielding anthraquinone (0·058 g., 100%), m. p. 277—278° (Found: C, 80·6; H, 3·9%).

Reactions of 2-*Hydroxy- and* 2-*Methoxy*-1 : 4-*naphthaquinones with Butadiene*.—2-Hydroxy-1 : 4-naphthaquinone (0·5 g.), butadiene (2 c.c.), and ethanol (30 c.c.) were heated at 135—140° for 65 hr. The deep orange solution, when evaporated, gave an intractable gum which was heated under reflux with potassium hydroxide (3 g.) and ethanol for 4 hr. The dark solution was then acidified, and the precipitate was collected, dried and sublimed *in vacuo*, giving pale yellow needles of anthraquinone (0·21 g., 35%), m. p. 278—280° (Found: C, 80·3; H, 3·9%). The infrared spectrum of the product was identical with that of authentic anthraquinone.

The reaction of 2-methoxy-1 : 4-naphthaquinone (0·5 g.), butadiene (2 c.c.), and benzene (20 c.c.) under the same conditions also gave anthraquinone (0·22 g., 33%).

11-*Acetoxy*-1 : 4 : 11 : 12-*tetrahydroanthraquinone*.—2-Acetoxy-1 : 4-naphthaquinone (0·5 g.), butadiene (5 c.c.), and benzene (15 c.c.) were heated at 100° for 150 hr., then evaporated to dryness. The residual gum was triturated with ethanol (5 c.c.). After several hours, rosettes of buff needles were collected, dried, and sublimed *in vacuo*, yielding 11-*acetoxy*-1 : 4 : 11 : 12-*tetrahydroanthraquinone* (VI; R = Ac) (0·52 g., 83%), needles, m. p. 146—147° (Found: C,

XUM

71·0; H, 5·3. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%), ν 5·75 and 5·9 μ, $\lambda_{max.}$ 2245, 3060 Å (log ε 4·5, 3·3 respectively).

The adduct (0·25 g.), sodium methoxide (1·0 g.), and methanol (10 c.c.) were heated under reflux for 12 hr. A buff solid separated later at 0°; this was collected and worked up as in previous experiments, giving anthraquinone (0·06 g., 33%), m. p. 275—277° (Found: C, 80·4; H, 4·0%).

1 : 4-*Dihydroanthraquinone*.—2-Acetoxy-1 : 4-naphthaquinone (0·5 g.), butadiene (5 c.c.), and benzene (20 c.c.) were heated at 130° for 150 hr., then evaporated to dryness. The semi-crystalline residue, recrystallised from light petroleum–benzene, yielded 1 : 4-dihydroanthraquinone (10·24 g., 32%), yellow needles darkening in air, m. p. 215—217° (decomp.) (Diels and Alder [5] give m. p. 209—210°) (Found: C, 80·0; H, 4·8. Calc. for $C_{14}H_{10}O_2$: C, 80·1; H, 4·9%). Treatment with alkali as in previous experiments gave anthraquinone.

1 : 4 : 11 : 12-Tetrahydroanthraquinone, prepared by the method of Diels and Alder,[5] had ν 5·9, $\lambda_{max.}$ 2250, 3000 Å (log ε 4·4, 3·2 respectively).

11-*Acetoxy*-1 : 4 : 11 : 12-*tetrahydro*-1 : 4-endo*methyleneanthraquinone*.—2-Acetoxy-1 : 4-naphthaquinone (0·5 g.), freshly prepared *cyclo*pentadiene (2 c.c.), and benzene (5 c.c.) were heated at 130° for 74 hr. The colourless solution, when cooled, deposited a solid which was collected and recrystallised from benzene, yielding 11-*acetoxy*-1 : 4 : 11 : 12-*tetrahydro*-1 : 4-endo*methyleneanthraquinone* (VII) (0·33 g.) as rhombs, m. p. 197—199° (Found: C, 72·7; H, 5·1. $C_{17}H_{14}O_4$ requires C, 72·4; H, 5·0%), ν 5·8, 5·95 μ, $\lambda_{max.}$ 2300, 3000 Å (log ε 4·2, 3·15 respectively). Evaporation of the mother-liquor to dryness and treatment of the residual gum with benzene gave another 0·08 g. of the adduct (total yield 63%). The adduct distilled unchanged at atmospheric pressure.

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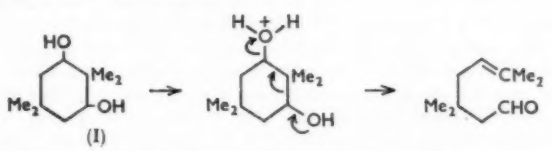
436. *Alicyclic Diketones and Diols. Part II.* The Dehydration of* cis- *and* trans-2 : 2 : 5 : 5-*Tetramethylcyclohexane*-1 : 3-*diol.*

By A. W. ALLAN, R. P. A. SNEEDEN, and (in part) J. M. WILSON.

Dehydration of *cis*- and *trans*-2 : 2 : 5 : 5-tetramethyl*cyclo*hexane-1 : 3-diol with potassium hydrogen sulphate has been shown to give 1 : 1-dimethyl-3-*iso*propylidene*cyclo*pent-2-ene, 2 : 3 : 5 : 5-tetramethyl*cyclo*hexanone, and 2 : 2 : 5 : 5-tetramethyl*cyclo*hex-3-enol. Syntheses of 1 : 1-dimethyl-3-*iso*propyl*cyclo*pentane, 2 : 3 : 5 : 5-tetramethyl*cyclo*hex-2-enone, and 2 : 2 : 5 : 5-tetramethyl*cyclo*hexanol are described. The formation of the dehydration products is discussed with reference to the conformations of the diols.

THIS work was undertaken in order to establish whether a suitably substituted cyclic 1 : 3-diol (I) might,[1] by analogy with acyclic compounds,[2] undergo dehydration to the unsaturated open-chain aldehyde, thus:



(I)

The preparation of pure *cis*- and *trans*-2 : 2 : 5 : 5-tetramethyl*cyclo*hexane-1 : 3-diol (I) has already been described,[3] and dehydration of either of these compounds with potassium

* Part I, *J.*, 1958, 557.

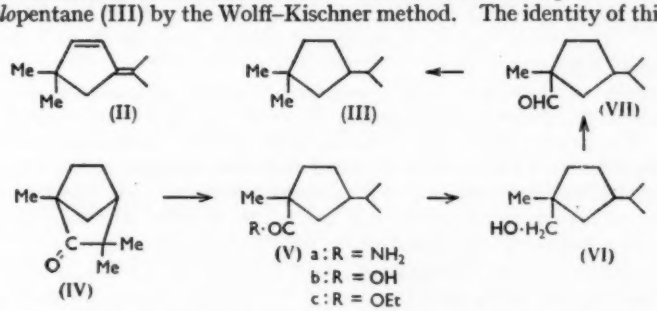
[1] Cf. English, Russel, and Brutcher, *J. Amer. Chem. Soc.*, 1950, **72**, 1653.
[2] English and Brutcher, *ibid.*, 1952, **74**, 4280.
[3] Allan, Sneeden, and (in part) Colvin, *J.*, 1958, 557.

hydrogen sulphate gave an oil and water. In both cases the infrared spectrum indicated that the oil consisted of a mixture of an unsaturated hydrocarbon, a carbonyl compound, and an alcohol. Attempted separations based on the preferential removal of the carbonyl compound were unsatisfactory. Chromatography of the reaction product, with *iso*-pentane as the initial solvent, effected separation into a hydrocarbon, a ketone, and an alcohol. A comparison of the infrared spectra and the retention times on vapour-phase chromatography showed that identical hydrocarbons, ketones, and alcohols were obtained from both diols. The percentages by weight present in the oil were:

	trans-Diol	*cis*-Diol
Unsat. hydrocarbon	53	88
Ketone	30	12
Alcohol	17	

The hydrocarbon $C_{10}H_{16}$ was rapidly oxidised in air and was shown to contain two double bonds by catalytic reduction to the saturated hydrocarbon $C_{10}H_{20}$. It was thus a *cyclo*alkadiene. It did not give a crystalline adduct with maleic anhydride, but the ultra-violet spectrum ($\lambda_{max.}$ 243 mμ; ε 12,500) indicated the presence of a conjugated diene system with only one double bond in a ring. Further, its infrared spectrum (see p. 2189) and the isolation of acetone (as 2 : 4-dinitrophenylhydrazone) after ozonolysis indicated structure (II). This was confirmed when it was shown that the derived saturated hydrocarbon was identical with 1 : 1-dimethyl-3-*iso*propyl*cyclo*pentane (III) prepared by the annexed route.

The structure of fencholamide (Va), the product obtained by the action of sodamide on fenchone,[4] has been rigorously established.[5] Semmler [4] converted it into the aldehyde (VII) by the route (Va, b, c), (VI), and (VII). In the present work many improvements were made on this synthesis. Thus the amide, which resists normal hydrolysis, was converted smoothly and rapidly into the acid by nitrous acid;[6] lithium aluminium hydride reduced the acid to the alcohol in excellent yield. Attempts to convert the alcohol into the hydrocarbon (III) by reduction of the toluene-*p*-sulphonate with lithium aluminium hydride [7] or by conversion into the chloro-compound and subsequent reduction,[8] led to products contaminated with unsaturated material However, chromic acid oxidised the alcohol, giving the aldehyde and, since the latter underwent rapid oxidation in air, it was isolated as its semicarbazone. This was reduced to pure 1 : 1-dimethyl-3-*iso*propyl*cyclo*pentane (III) by the Wolff–Kischner method. The identity of this substance

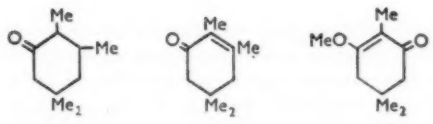


and the hydrocarbon $C_{10}H_{20}$ was established by a comparison of their infrared spectra and their refractive indices, and they showed identical "cracking-patterns" in the mass spectrometer.*

* Specimens of hydrocarbon obtained by Huang-Minlon reduction of the aldehyde gave infrared spectra which were almost identical with that of the hydrocarbon $C_{10}H_{20}$, but their "cracking-patterns" in the mass spectrometer indicated substantial quantities of impurities.

[4] Semmler, *Ber.*, 1906, **39**, 2578.
[5] Bouveault and Levallois, *Bull. Soc. chim. France*, 1910, **7**, 683, 736, 807.
[6] Cf. Carter and Slater, *J.*, 1946, 130.
[7] Cf. Birch and Dean, *J.*, 1953, 2477.
[8] Cf. Komppa and Klami, *Ber.*, 1935, **68**, 2001.

The ketone $C_{10}H_{18}O$, purified through its oxime, showed no selective ultraviolet absorption, but the ultraviolet spectrum of its 2 : 4-dinitrophenylhydrazone (see p. 2190) indicated[9] that it was probably a substituted *cyclo*hexanone, and this was confirmed by the infrared spectrum of the ketone ($\nu_{max.}$ 1705 cm.$^{-1}$, six-membered ring ketone). The most probable structure for the ketone is therefore 2 : 3 : 5 : 5-tetramethyl*cyclo*hexanone (VIII). The ketone was converted into the corresponding αβ-unsaturated ketone by bromination and subsequent dehydrobromination with 2 : 4-dinitrophenylhydrazine in acetic acid.[10] The 2 : 4-dinitrophenylhydrazone obtained in this way was identical with that of synthetic 2 : 3 : 5 : 5-tetramethyl*cyclo*hex-2-enone (IX). Since it can be assumed that the above reactions proceed without rearrangement, the structure of the ketone $C_{10}H_{18}O$ is thereby established as (VIII).



(VIII) (IX) (X)

2 : 3 : 5 : 5-Tetramethyl*cyclo*hex-2-enone (IX) was prepared by the action of methylmagnesium iodide on the methyl enol ether (X) and treatment of the product with acid. The pure ketone prepared in this way showed $\lambda_{max.}$ 244 mμ (ε 15,200) whereas Conia[11] records $\lambda_{max.}$ 247 mμ (ε 9600) for the same substance prepared by the methylation of *iso*phorone. A direct comparison of the 2 : 4-dinitrophenylhydrazones of our ketone with that prepared from Conia's ketone indicated that the two derivatives were identical.

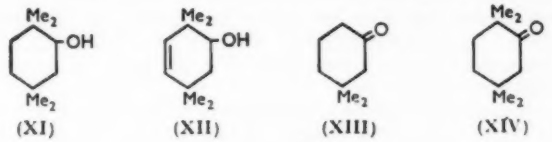
The alcohol fraction gave, on chromatography, a crude crystalline alcohol whose infrared spectrum indicated the presence of a hydroxyl group and a *cis*-double bond. The unsaturated alcohol was purified as its hydrogen phthalate, and owing to the small quantities available this was reduced catalytically. The only catalyst to effect reduction was platinum oxide, with the result that the uptake was far in excess of 1 mol. (presumably owing to concomitant hydrogenation in the phthaloyl residue). Hydrolysis of the reduction product furnished a crystalline saturated alcohol $C_{10}H_{20}O$ (purified through its hydrogen phthalate) identical with a synthetic specimen of 2 : 2 : 5 : 5-tetramethyl*cyclo*hexanol (XI). It follows that the unsaturated alcohol must be 2 : 2 : 5 : 5-tetramethyl*cyclo*hex-3-enol (XII).

3 : 3-Dimethyl*cyclo*hexanone (XIII), prepared by a new method, was methylated with methyl iodide in the presence of sodamide, the crude product being purified as its semicarbazone. The ketone (XIV) on reduction with lithium aluminium hydride gave the tetramethyl*cyclo*hexanol (XI). It is assumed that the methylation occurs at position 2 since treatment of dihydro*iso*phorone with *iso*pentyl formate in the presence of base gives the 2-hydroxymethylene compound as sole product.[12] Further, the original diol (I) could not give rise to a *cyclo*hexyl compound with a substituent in the 6-position.

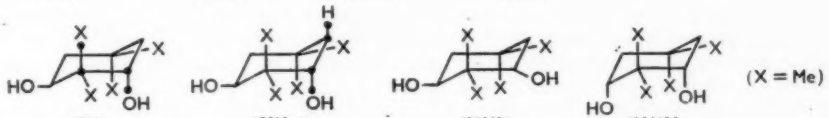
With the structure of the dehydration products established it is of interest to consider their formation in terms of the conformations of the original diols. The *trans*-diol can only have the conformation (XV), or its mirror image, whilst the *cis*-diol can have either the conformation (XVI) (both hydroxyl groups equatorial) or (XVII) (both hydroxyl groups axial). The infrared spectrum of the *cis*-diol, in carbon tetrachloride solution, showed only one band in the hydroxyl region ($\nu_{max.}$ 3635 cm.$^{-1}$); the *trans*-diol had $\nu_{max.}$ 3637 cm.$^{-1}$. It follows that the *cis*-diol, in contrast to *cis-cyclo*hexane-1 : 3-diol,[13] is free from internal hydrogen bonding, and that the preferred conformation is the diequatorial (XVI). This

[9] Cf. Braude and Jones, *J.*, 1945, 498.
[10] Cf. Mattox and Kendal, *J. Amer. Chem. Soc.*, 1948, **70**, 882.
[11] Conia, *Bull. Soc. chim. France*, 1954, 690.
[12] Ruzicka, Shinz, and Seidel, *Helv. Chim. Acta*, 1940, **23**, 935.
[13] Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492.

is probably due to the fact that in the diaxial form (XVII) the " 1 : 3-interaction " of the hydroxyl groups and the axial 5-methyl group renders this form less stable than the diequatorial one. The formation of the rearranged product (II) can readily be explained,

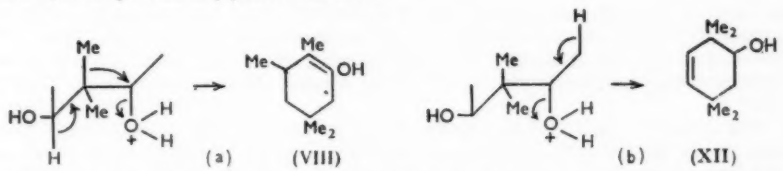


(XI) (XII) (XIII) (XIV)



(XV) (XVa) (XVI) (XVII) (X = Me)

since in both diols the steric arrangements are propitious for dehydration accompanied by ring contraction.[14] That the *trans*-diol yields *substantial* quantities of the ketone (VIII) and the alcohol (XII), can be related to the fact that in this compound there must be two other " four-body planar systems " (XV) and (XVa), not normally present in the *cis*-diol (XVI). Dehydrations involving the axial hydroxyl group would lead by scheme (a) to the ketone, and by scheme (b) to the alcohol.



(a) (VIII) (b) (XII)

Similarly the formation of *small* quantities of the ketone (VIII) and the alcohol (XII) on dehydration of the *cis*-diol can be regarded as arising from reactions involving the diol in the less stable diaxial conformation (XVII). It is of interest that no product indicative of ring fission was detected. Since completion of this work, Brutcher and Cenci [15] have reported that the dehydration of *cis*- and *trans-cyclo*hexane-1 : 3-diol with potassium hydrogen sulphate gives a mixture of *cyclo*hexane derivatives and no open-chain compound.

Experimental

The rotations and ultraviolet absorption spectra were taken for ethanol solutions, and all the m. p.s are corrected. The intensities of the infrared absorption bands are indicated qualitatively by the symbols s (strong), m (medium), and w (weak).

Dehydration of cis- *and* trans-2 : 2 : 5 : 5-*Tetramethyl*cyclo*hexane*-1 : 3-*diol.—General method.* The crushed diol (4 g.), mixed with freshly fused potassium hydrogen sulphate (8 g.) and kieselguhr (2 g.), was packed in a combustion tube and covered with a mixture of freshly fused potassium hydrogen sulphate (4 g.) and kieselguhr (1 g.). The tube, in a horizontal position, was connected to a receiver (cooled in acetone–carbon dioxide), and the apparatus was evacuated at the water-pump. The end of the tube containing the reaction mixture was heated at 170—190° for 5 hr. The receiver was then disconnected and the product purified.

trans-*Diol.* The dried product (3·2 g.) in *iso*pentane was chromatographed on alumina. Elution with *iso*pentane gave 1 : 1-*dimethyl*-3-iso*propylidene*cyclo*pent*-2-*ene* (II) (1·70 g.), b. p. 28—30°/1·7 mm., n_D^{20} 1·4730 (Found: C, 87·9; H, 12·0. $C_{10}H_{16}$ requires C, 88·2; H, 11·8%), $\lambda_{max.}$ 243 (ε 12,500), $\nu_{max.}$ (thin film) 1620, 1600 (w, diene system), 1370, 1360 (s, $-CMe_2$), 816 (s, C=C), and 768 cm.$^{-1}$ (s, *cis* −CH=CH−). Elution with ether gave 2 : 3 : 5 : 5-tetramethyl*cyclo*hexanone

[14] Barton, *J.*, 1953, 1027 and references cited therein.
[15] Brutcher and Cenci, *Diss. Abs.*, 1958, **18**, 393.

(VIII), purified as its *oxime*, prisms [from light petroleum (b. p. 60—80°)] (1·07 g.), m. p. 136—137° (Found: C, 71·0; H, 11·15; N, 8·2. $C_{10}H_{19}ON$ requires C, 71·0; H, 11·3; N, 8·3%). The latter on hydrolysis with dilute hydrochloric acid gave the *ketone* (0·87 g.), b. p. 52—54°/1·5 mm., n_D^{21} 1·4510 (Found: C, 77·6; H, 11·5. $C_{10}H_{18}O$ requires C, 77·9; H, 11·8%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol as red prisms, m. p. 132—134° (Found: C, 57·4; H, 6·5; N, 16·7. $C_{16}H_{22}O_4N_4$ requires C, 57·5; H, 6·6; N, 16·8%), $\lambda_{max.}$ 229 (ε 18,700), 265 (ε 10,500), and 361 mμ (ε 23,200). Elution with ether–methanol gave an oil from which the unsaturated alcohol (XII) was isolated.

cis-*Diol*. Chromatography of the dried product (2 g.) gave the diene (II) (1·8 g.) and the ketone (VIII), with infrared spectra identical with those of the compounds obtained from the *trans*-diol. There was also obtained a third fraction from which the alcohol (XII) was isolated.

Hydrogenation of the Diene $C_{10}H_{16}$.—The diene (II) (0·88 g.) in acetic acid solution over Adams catalyst (100 mg.) absorbed 312 c.c. of hydrogen (2 mol.). Neutralisation with sodium hydroxide solution, followed by distillation of the dried hydrocarbon layer, gave 1 : 1-*dimethyl*-3-iso*propyl*cyclo*pentane*, b. p. 148—149°, n_D^{20} 1·4267 (Found: C, 85·2; H, 14·6. $C_{10}H_{20}$ requires C, 85·6; H, 14·4%).

Ozonolysis of the Diene $C_{10}H_{16}$.—The diene (II) (1·0 g.) in pure anhydrous ethyl acetate (17 c.c.), at −75°, was subjected to a stream of ozone. When all had reacted (4½ hr.), as indicated by the tetranitromethane test, the solution was evaporated at 2 mm., water (10 c.c.) was added, and the whole heated under reflux for 2 hr. before distillation. After neutralisation of the distillate with sodium hydroxide solution, the neutral products and water were co-distilled directly into a solution of 2 : 4-dinitrophenylhydrazine (2 g.) in ethanol (50 c.c.) containing concentrated sulphuric acid (20 c.c.). The crude 2 : 4-dinitrophenylhydrazone (1·72 g.), m. p. 94—95°, was chromatographed on a column of bentonite (120 g.) and kieselguhr (30 g.) to give, by elution with chloroform, an unidentified 2 : 4-dinitrophenylhydrazone (0·345 g.), m. p. 162—165°, as red prisms (from ethanol), and by elution with chloroform–methanol (10 : 1) acetone 2 : 4-dinitrophenylhydrazone (0·722 g.) as yellow needles (from ethanol), m. p. and mixed 124—125°.

(+)-*Fencholamide* (Va).—(+)-Fencholamide was prepared by the action of freshly prepared sodamide [(from sodium (14 g.)] on fenchone (100 g.), $[\alpha]_D^{18}$ +69·0° (*c* 1·45), by Semmler's method.[4] The pure amide (125 g.) crystallised from methanol as plates, m. p. 100—101°, $[\alpha]_D^{18}$ +1·4° (*c* 2·09). For this substance von Braun and Jacobs [16] record m. p. 116°, and state "the amide is optically inactive;" Wallach [17] records m. p. 94° and "a low positive rotation;" Semmler [4] reports m. p. 94° and makes no mention of the rotation.

(+)-*Fencholic Acid*.—A saturated solution of sodium nitrite (70 g.) in water [final total volume (150 c.c.)] was added with stirring to a cooled solution of (+)-fencholamide (125 g.) in concentrated sulphuric acid (600 c.c.). The reactants were warmed on the water-bath until evolution of nitrogen ceased. Water was added to the cooled solution, and the products were extracted with ether. The acid which was isolated by extraction with sodium hydroxide solution, acidification, and extraction with ether gave on distillation (+)-fencholic acid (60 g.), b. p. 116—118°/0·5 mm., n_D^{21} 1·4558, $[\alpha]_D^{19}$ +3·97° (*c* 7·6) (lit.,[17] b. p. 151—152°/17 mm., n_D^{20} 1·4563, $[\alpha]_D$ +4·17°).

(+)-*Dihydrofenchyl Alcohol* (VI).—(+)-Fencholic acid (54 g.) in dry ether (500 c.c.) was added slowly to a suspension of lithium aluminium hydride (29 g.) in dry ether (600 c.c.), and the whole heated under reflux for 2 hr. The product isolated in the usual manner gave, on fractionation, the alcohol (VI), b. p. 84°/0·5 mm., n_D^{18} 1·4560, $[\alpha]_D^{20}$ +12·25° (*c* 4·65) (Found: C, 77·1; H, 12·9. Calc. for $C_{10}H_{20}O$: C, 76·9; H, 12·9%) (lit.,[4] b. p. 100°/11 mm., n_D 1·4566).

(+)-*Dihydrofencholaldehyde* (VII).—(+)-Dihydrofenchyl alcohol (5 g.) in benzene (50 c.c.) was added to potassium dichromate (5 g.) in water (55 c.c.) containing concentrated sulphuric acid (6 g.) and shaken vigorously for 4 hr. under carbon dioxide. Fractional distillation of the washed and dried ($MgSO_4$) organic layer gave the aldehyde (VII) (2·65 g.), b. p. 50—54°/0·5 mm., n_D^{24} 1·4460 (lit.,[4] b. p. 80—85°/10 mm., n_D 1·445). The semicarbazone was obtained from benzene as needles, m. p. 152—153° (Found: C, 62·2; H, 10·1. Calc. for $C_{11}H_{21}ON_3$: C, 62·5; H, 10·0%) (lit.,[4] m. p. 144—145°). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol as red prisms, m. p. 123—124° (Found: C, 57·6; H, 6·7; N, 16·5. $C_{16}H_{22}O_4N_4$ requires C, 57·5; H, 6·6; N, 16·8%).

[16] von Braun and Jacobs, *Ber.*, 1933, **66**, 1461.
[17] Wallach, *Ann.*, 1910, **369**, 63.

(+)-1 : 1-*Dimethyl*-3-iso*propyl*cyclo*pentane* (III).—The semicarbazone (3·36 g.) of the aldehyde (VII) was heated slowly with potassium hydroxide (7·5 g.) until nitrogen was evolved (200°). This temperature was maintained until all the hydrocarbon had distilled (1 hr.). Distillation of the product, after it had been washed with dilute sulphuric acid and dried, gave the hydrocarbon (III), b. p. 148—149°, n_D^{21} 1·4240, $[\alpha]_D^{20}$ +2·94° (*c* 1·46). The infrared spectra of this and the hydrocarbon $C_{10}H_{20}$ were superposable.

Bromination and Dehydrobromination of the Ketone (VIII).—The ketone (0·320 g.) in acetic acid (10 c.c.) was treated slowly with bromine (1 mol.) in acetic acid. The colourless solution was treated with 2 : 4-dinitrophenylhydrazine (0·388 g.) also in acetic acid, and the reactants were warmed on the steam-bath for 5 min. The product, m. p. 173—174°, obtained by precipitation with water, gave on recrystallisation from ethanol 2 : 3 : 5 : 5-*tetramethyl*cyclo*hex*-2-*enone* 2 : 4-*dinitrophenylhydrazone* (0·14 g.) as red plates, m. p. 175—177°, alone or admixed with a specimen prepared as below (Found: C, 57·8; H, 6·1; N, 16·7. $C_{15}H_{20}O_4N_4$ requires C, 57·8; H, 6·1; N, 16·9%).

3-*Methoxy*-2 : 5 : 5-*trimethyl*cyclo*hex*-2-*enone* (X).—This *ether*, obtained by the action [18] of excess of diazomethane on 2 : 5 : 5-trimethyl*cyclo*hexane-1 : 3-dione, crystallised from light petroleum (b. p. 60—80°) as prisms, m. p. 55—58° (Found: C, 71·25; H, 9·8. $C_{10}H_{16}O_3$ requires C, 71·4; H, 9·6%).

2 : 3 : 5 : 5-*Tetramethyl*cyclo*hex*-2-*enone* (IX).—The enol ether (X) (3·2 g.) in dry ether (10 c.c.) was added slowly to a freshly prepared solution of methylmagnesium iodide [from magnesium (1·86 g.)] in dry ether (15 c.c.) and heated under reflux for 6 hr. (experiments at 0° and at room temperature were not successful). Fractional distillation of the product, isolated in the usual manner, gave the ketone (IX) (1·5 g.), b. p. 65—67°/18 mm., n_D^{18} 1·4830 (Found: C, 79·0; H, 10·6. Calc. for $C_{10}H_{16}O$: C, 78·9; H, 10·6%), $\lambda_{max.}$ 244 mμ (ε 15,200) [lit.,[11] b. p. 90°/8 mm., n_D^{21} 1·4798, $\lambda_{max.}$ 247 mμ (ε 9600)]. The 2 : 4-dinitrophenylhydrazone crystallised from ethanol as red plates, m. p. 175—177°, alone or mixed with either the derivative prepared as above or with the derivative of Conia's ketone; [11] the infrared spectra of the three specimens were superposable.

Isolation of the Third Dehydration Product.—Several combined third fractions (1·63 g.) (see above, purification of the dehydration product) were chromatographed on alumina to give: (i) by elution with light petroleum (b. p. 40—60°) a mixture (0·17 g.) of ketone (VIII) and an alcohol; (ii) by elution with light petroleum (b. p. 40—60°)–ether (5 : 1) a crystalline alcohol (0·51 g.); and (iii) by elution with ether–methanol a mixture (0·73 g.) of the alcohol and unchanged diol (identified by its infrared spectrum). The infrared spectrum of the alcohol of m. p. 44—45°, $\nu_{max.}$ 3240 (s, OH), 1710 (w, C=O in 6-membered rings), and 768 $cm.^{-1}$ (s, *cis* –CH=CH–), indicated that it was unsaturated and contained a trace of ketone. The *hydrogen phthalate* of (XII) crystallised from acetic acid as prisms, m. p. 153·5—154·5° (Found: C, 71·5; H, 6·85. $C_{18}H_{22}O_4$ requires C, 71·5; H, 7·3%). This derivative (0·93 g.) was hydrogenated in ethanol solution over Adams catalyst (0·1 g.), the hydrogenation being stopped after absorption of 3·6 mols. of hydrogen. Water (3 c.c.) and potassium hydroxide (3 g.) were added to the filtered solution and the whole was heated under reflux for 3 hr. The product, isolated with the aid of ether, was converted into its hydrogen phthalate, which on recrystallisation from aqueous acetic acid gave the 2 : 2 : 5 : 5-*tetramethyl*cyclo*hexyl hydrogen phthalate* (cf. XI) as prisms, m. p. 168·5—170·5° (Found: C, 71·4; H, 8·1. $C_{18}H_{24}O_4$ requires C, 71·0; H, 7·95%). This derivative with aqueous potassium hydroxide (10 c.c. of 10%) and subsequent sublimation of the product gave 2 : 2 : 5 : 5-*tetramethyl*cyclo*hexanol* (XI), prisms, m. p. 54—56° (Found: C, 76·6; H, 13·2. $C_{10}H_{20}O$ requires C, 76·9; H, 12·9%).

5 : 5-*Dimethyl*cyclo*hex*-2-*enone*.—3-iso*Butoxy*-5 : 5-*dimethyl*cyclo*hex*-2-*enone* (60 g.), prepared from dimedone by the method of Eschenmoser *et al.*,[19] b. p. 76°/0·1 mm., n_D^{18} 1·4810 (Found: C, 73·45; H, 9·8. $C_{12}H_{20}O_2$ requires C, 73·4; H, 10·3%), was reduced with lithium aluminium hydride (5 g.) in ether to give, by the usual isolation procedure, 5 : 5-dimethyl*cyclo*hex-2-enone, b. p. 76°/16 mm., n_D^{22} 1·4699 (lit.,[20] b. p. 75°/15 mm., n_D^{20} 1·4710). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol as red prisms, m. p. 161—163° (Found: C, 55·5; H, 5·35; N, 18·4. $C_{14}H_{16}O_4N_4$ requires C, 55·25; H, 5·3; N, 18·4%).

3 : 3-*Dimethyl*cyclo*hexanone* (XIII).—The above ketone (5 g.) in ethanol (50 c.c.) was

[18] Cf. Born, Pappo, and Szmuszkovicz, *J.*, 1953, 1779.
[19] Eschenmoser, Schreiber, and Julia, *Helv. Chim. Acta*, 1953, **36**, 482.
[20] Frank and Hall, *J. Amer. Chem. Soc.*, 1950, **72**, 1645.

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hydrogenated over 10% palladised charcoal (0·5 g.). Hydrogen (1 mol.) was rapidly absorbed and fractionation of the filtered solution gave the ketone (XIII), b. p. 44—45°/1·5 mm., $\nu_{max.}$ 1710 cm.$^{-1}$ (s, C=O in a 6-membered ring).

2 : 2 : 5 : 5-*Tetramethyl*cyclo*hexanone* (XIV).—The ketone (XIII) (2·82 g.) in dry ether (10 c.c.) was added to a freshly prepared suspension of sodamide [(from sodium (1·03 g.)] in dry ether (30 c.c.) and heated under reflux for 1½ hr. Methyl iodide (7·35 g.) in an equal volume of dry ether was added slowly with stirring to the cold solution, and the whole subsequently heated under reflux for 4 hr. The product (3·3 g.), isolated in the usual manner, was shown, by vapour-phase chromatography, to contain an impurity. The semicarbazone was prepared and repeated crystallisation from benzene–ethanol finally gave the *semicarbazone* (1·82 g.) of the ketone (XIV) as prisms, m. p. 198·5—201·5° (Found: C, 62·7; H, 10·5. $C_{11}H_{21}ON_3$ requires C, 62·5; H, 10·0%). This on hydrolysis with dilute mineral acid gave 2 : 2 : 5 : 5-*tetramethyl*cyclo*hexanone* (XIV) (1·3 g.), b. p. 98°/46 mm., n_D^{19} 1·4448 (Found: C, 77·2; H, 11·65. $C_{10}H_{18}O$ requires C, 77·9; H, 11·8%). The 2 : 4-*dinitrophenylhydrazone* crystallised from chloroform–ethanol as red plates, m. p. 169—171° (Found: C, 57·2; H, 6·65. $C_{16}H_{22}O_4N_4$ requires C, 57·5; H, 6·6%).

2 : 2 : 5 : 5-*Tetramethyl*cyclo*hexanol* (XI).—The ketone (XIV) (0·88 g.) in dry ether (10 c.c.) was added to a suspension of lithium aluminium hydride (0·5 g.) in dry ether (25 c.c.) and heated under reflux for 1 hr. The product isolated in the usual manner gave, on distillation, 2 : 2 : 5 : 5-tetramethyl*cyclo*hexanol, m. p. and mixed m. p. 52—54°. The infrared spectra of this and the specimen prepared as above were superposable. The hydrogen phthalate crystallised from ethanol as prisms, m. p. 169·5—171·5°, alone or mixed with the specimen obtained above, and the infrared spectra of the two specimens were superposable.

One of us (A. W. A.) is indebted to the Department of Scientific and Industrial Research for a maintenance allowance. Some of the infrared spectra were determined by Dr. G. Eglinton and his associates and the analyses were kindly carried out by Mr. J. M. L. Cameron and his associates. The authors also thank Dr. R. I. Reed and Mr. W. Sneddon for obtaining and interpreting the mass-spectral data, and Professor J. Conia for the generous gift of a specimen of his 2 : 3 : 5 : 5-tetramethyl*cyclo*hex-2-enone.

THE UNIVERSITY, GLASGOW, W.2. [*Received, February 2nd*, 1959.]

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437. *Synthesis of Cytidine Diphosphate Ribitol.*

By J. BADDILEY, J. G. BUCHANAN, and C. P. FAWCETT.

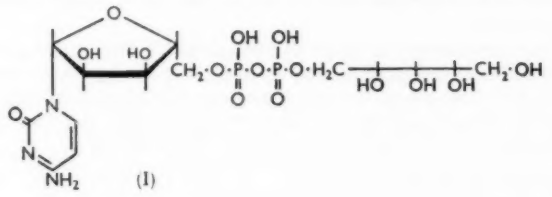
Cytidine-5′ phosphate and ribose 5-phosphate, in the presence of dicyclohexylcarbodi-imide, gave P^1-cytidine-5′ P^2-ribose 5-pyrophosphate (III). Reduction of this nucleotide with sodium borohydride at pH 8·5—9·2 gave cytidine diphosphate ribitol (I) indistinguishable from the natural material.

CYTIDINE DIPHOSPHATE RIBITOL (CDP-ribitol) (I) was first detected[1] in *Lactobacillus arabinosus* and has been isolated from that source.[2] Its presence in other Gram-positive organisms and its function in the biosynthesis of a new group of cell-wall components, the teichoic acids, have been discussed recently.[3] As only very small amounts of material were available for structural studies, much of the evidence[4,5] for the formula (I) is based on paper chromatography. A synthesis would be valuable, not only in confirming the structure, but also in the hope that material would thereby be available for studies on the biosynthesis of the teichoic acids.

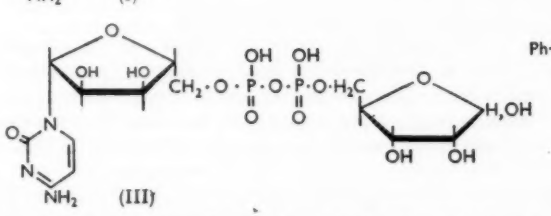
* The nomenclature adopted here for ribitol phosphates is discussed in ref. 5. This compound is, systematically, L-ribitol 1-phosphate.

[1] Baddiley and Mathias, *J.*, 1954, 2723.
[2] Baddiley, Buchanan, Carss, Mathias, and Sanderson, *Biochem. J.*, 1956, **64**, 599.
[3] Armstrong, Baddiley, Buchanan, and Carss, *Nature*, 1958, **181**, 1692; Armstrong, Baddiley, Buchanan, Carss, and Greenberg, *J.*, 1958, 4344.
[4] Baddiley, Buchanan, Carss, and Mathias, *J.*, 1956, 4583.
[5] Baddiley, Buchanan, and Carss, *J.*, 1957, 1869.

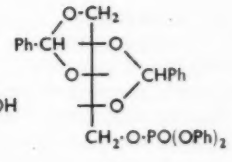
During work on the synthesis of the related nucleotide, cytidine diphosphate glycerol,[6] it was found that mixtures of polyol phosphates and nucleoside-5′ phosphates do not yield the unsymmetrically substituted pyrophosphates in the presence of dicyclohexylcarbodi-imide. The ready cyclisation of the phosphate group situated adjacent to a hydroxyl group in the acyclic polyol phosphate leads to exclusive formation of the cyclic phosphate: the nucleoside-5′ phosphate in these mixtures is largely converted into the dinucleoside pyrophosphate. This difficulty was surmounted in the CDP-glycerol synthesis by protection of the hydroxyl groups in α-glycerophosphate with an isopropylidene residue.



(I)



(III)



(II)

For a synthesis of CDP-ribitol along similar lines to those adopted in the synthesis of CDP-glycerol, it would be necessary to protect most or all the hydroxyl groups in D-ribitol 5-phosphate * with residues which could be removed under mild conditions. In a model experiment 1,3:2,4-dibenzylidenexylitol readily gave a 5-(diphenyl phosphate) (II) when treated with diphenyl phosphorochloridate in pyridine, but much difficulty was encountered in the attempted removal of both phenyl groups from this ester. Moreover, although it was possible to remove one benzyl group from the corresponding dibenzyl ester by anionic debenzylation, removal of the second benzyl group without loss of benzylidene residues was troublesome.

An alternative synthesis, which would also avoid the difficulty of resolution of racemates, starts from D-ribose 5-phosphate. The presence of the furanose ring in ribose 5-phosphate considerably reduces the possibility of cyclic phosphate formation under normal procedures for pyrophosphate synthesis.[7] In this connexion, good yields of dinucleoside pyrophosphates and nucleoside pyro- and tri-phosphates have been obtained by the carbodi-imide method on nucleotides. Even ribose 5-phosphate itself has been used successfully in this way for the synthesis of its pyro- and tri-phosphate.[8]

P^1-Cytidine-5′ P^2-ribose 5-pyrophosphate (III) (CDP-ribose) was prepared from cytidine-5′ phosphate and ribose 5-phosphate by reaction with dicyclohexylcarbodi-imide in pyridine containing a small amount of tri-n-butylamine.[9] The pyrophosphate (III), isolated as its ammonium salt by ion-exchange chromatography, was homogeneous when examined by paper chromatography and showed properties consistent with the presence of a free reducing centre in the ribose phosphate residue. It was hydrolysed by acids to cytidine-5′ phosphate and ribose 5-phosphate, both identified by paper chromatography.

CDP-ribose was smoothly reduced to CDP-ribitol by sodium borohydride in a glycine buffer between pH 8·5 and 9·2, though careful control of reaction conditions was necessary

[6] Baddiley, Buchanan, and Sanderson, *J.*, 1958, **3107**.
[7] Baddiley, Buchanan, and Szabo, *J.*, 1954, **3826**.
[8] Horecker, Hurwitz, and Heppel, *J. Amer. Chem. Soc.*, 1957, **79**, 701.
[9] Cf. Smith and Khorana, *ibid.*, 1958, **80**, 1141.

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to avoid decomposition of the product. CDP-ribitol is known to be very labile towards both acid and alkali. Borate and other ions and buffer components were removed by adsorption of the nucleotide on a charcoal column. The liberation and subsequent removal of borate from its complex with the product was not complete under conditions similar to those described by Whelan and Morgan [10] for its removal from carbohydrate mixtures. However, exhaustive washing of the charcoal with water adjusted to pH 3·8 removed all but the last trace of borate. 2·5% of the natural nucleotide was hydrolysed at 20° and pH 3 in 18 hr. The lability of this nucleotide towards acid was apparent from a similar experiment at pH 2, where 19% of hydrolysis occurred. At lower pH values hydrolysis was complete under these conditions.

CDP-ribitol was isolated as its ammonium salt. Although it contained about 5% of cytidine-5′ phosphate, the synthetic compound was considerably purer than the best samples of the natural material. It was indistinguishable from the natural nucleotide on paper chromatograms, and was converted into cytidine-5′ phosphate and ribitol 4,5-(hydrogen phosphate) by treatment with ammonia: natural CDP-ribitol was known to give this cyclic phosphate under identical conditions.[4] It was hydrolysed by *Crotalus atrox* venom to cytidine, orthophosphate, and ribitol 5-phosphate.

Specific enzymic methods for the identification of CDP-ribitol are not yet adequately developed, but it is noteworthy that the synthetic product should be stereochemically identical with the natural nucleotide. The polyol phosphate residue in synthetic CDP-ribitol, having been derived from D-ribose 5-phosphate, will be D-ribitol 5-phosphate. It was shown earlier that the corresponding residue in natural CDP-ribitol is also D-ribitol 5-phosphate.[5]

The possibility that CDP-ribose (III) might have biological significance has not been investigated. Although a biosynthetic scheme for CDP-ribitol could involve reaction between cytidine triphosphate and ribose 5-phosphate, then reduction of the resulting CDP-ribose, there is no evidence yet to support this. On the contrary, CDP-ribitol has been prepared from cytidine triphosphate and ribitol 5-phosphate by an enzyme isolated from bacteria,[11] and it is likely that this would be the normal route for its biosynthesis.

Experimental

1,3:2,4-*Di*-O-*benzylidene*-DL-*xylitol* 5-(*Diphenyl Phosphate*).—Diphenyl phosphorochloridate (2·6 g.) was added with shaking to an ice-cold solution of 1,3:2,4-di-*O*-benzylidene-DL-xylitol [12] in dry pyridine (10 ml.). Pyridine hydrochloride soon settled and the mixture was kept at 0° overnight. A little water was added to decompose the excess of reagent, and then chloroform, and the solution was washed three times each with sodium hydrogen carbonate solution and water and dried (Na_2SO_4–$MgSO_4$). Solvents were removed *in vacuo* with the addition of small quantities of chloroform, then benzene, to remove traces of pyridine. The *ester* (2·6 g., 70%) was obtained as white crystals, m. p. 161°, by precipitation from chloroform by light petroleum (b. p. 60—80°) (Found: C, 65·6; H, 5·2; P, 5·5. $C_{31}H_{29}O_6P$ requires C, 66·3; H, 5·2; P, 5·5%).

Alkaline Hydrolysis.—The above ester (100 mg.) in dioxan (3 ml.) was shaken with 2N-sodium hydroxide (3 ml.) for 12 hr. Repeated evaporation with water was followed by addition of barium acetate solution, and the resulting precipitate (which contained a little barium silicate) was examined by paper chromatography in n-propyl alcohol–ammonia (*d* 0·88)–water (6 : 3 : 1). Two products, R_P 0·84 and 0·75, were detected by the phosphate spray reagents. The faster-moving product, believed to be the monophenyl ester, predominated; but under more prolonged conditions of hydrolysis the slower-moving product predominated. This is probably an ester in which both phenyl groups have been removed, but neither of the products was obtained in sufficient amount for adequate identification.

1,3:2,4-*Di*-O-*benzylidene*-DL-*xylitol* 5-(*Dibenzyl Phosphate*).—Dibenzyl phosphorochloridate (from 1·22 g. of dibenzyl phosphite) was added to a solution of dibenzylidenexylitol (1 g.) in dry

[10] Whelan and Morgan, *Chem. and Ind.*, 1955, 1449.
[11] Shaw, *Biochem. J.*, 1957, **66**, 56P.
[12] Ness, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1953, **75**, 132.

pyridine at −20°. The mixture was kept at 0° for 16 hr., then worked up in the usual manner. The resulting light brown gum was dissolved in a little alcohol, from which the ***dibenzyl ester*** (1·1 g.) crystallised. It was purified by chromatography on alumina (Grade 0; Peter Spence), the ester being eluted with 50% benzene–chloroform. It crystallised from alcohol with m. p. 93° (Found: C, 67·3; H, 5·5; P, 5·0. $C_{33}H_{35}O_8P$ requires C, 67·3; H, 5·6; P, 5·3%).

The dibenzyl ester (600 mg.) and barium iodide (300 mg.) were refluxed in dry acetone for 2·5 hr. After addition of water and extraction with ether (3 times), the aqueous solution was concentrated to about 20 ml.; crystallisation then began. The ***barium salt*** of the monobenzyl ester was obtained as white needles (0·5 g.) [Found: P, 5·5. $(C_{26}H_{26}O_8P)_2Ba$ requires P, 5·5%]. It was homogeneous, R_P 0·87, on paper chromatography in *n*-propyl alcohol–ammonia (*d* 0·88)–water (8 : 1 : 1).

P¹-*Cytidine*-5′ P²-*Ribose* 5-*Pyrophosphate* (*CDP-ribose*).—A solution of barium ribose 5-phosphate (260 mg.) in water was passed through a column (3 × 1 cm.) of Dowex-50 (H^+ form) resin, and eluate and washings were evaporated *in vacuo* to a gum. This was dissolved in water (1·0 ml.), and pyridine (10 ml.) was added. The solution was mixed with a solution of cytidine-5′ phosphate (190 mg.) in water (2 ml.) and pyridine (10 ml.) to which had been added tri-n-butylamine (0·5 ml.). Dicyclohexylcarbodi-imide (12 g.) in pyridine (20 ml.) was added and the mixture was shaken at room temperature for 30 hr. Cold water (50 ml.) was added and dicyclohexylurea was filtered off, then washed with water. The combined filtrate and washings were extracted with ether (6 times), aerated, adjusted to pH 7·5, and passed through a column (70 × 2·5 cm.) of Dowex-1 × 2 (chloride form; 200—400 mesh) resin. After washing of the column with water (500 ml.), gradient elution was carried out from a reservoir containing a solution (4·6 l.) which was 0·025M with respect to calcium chloride and 0·0032N with respect to hydrochloric acid (pH 2·5), and a mixing chamber containing 0·0001N-hydrochloric acid (400 ml.). The apparatus [13] was designed to give a concave gradient of chloride concentration and pH. Fractions (40 ml.) were collected automatically at a flow rate of 3 ml./min. Nucleotides were detected in fractions by their absorption at 280 mμ. Cytidine-5′ phosphate was collected in tubes 53—63, P^1P^2-dicytidine-5′ pyrophosphate in tubes 67—82, and CDP-ribose in tubes 135—162. The appropriate fractions were combined, neutralised with calcium hydroxide solution, concentrated at <35°, and freeze-dried. The ratio cytidine (calc. from ultraviolet absorption) : phosphorus in these combined fractions was 1 : 1, 1 : 1, and 1 : 2 respectively. Calcium chloride was removed from the freeze-dried material by extraction with alcohol, and the nucleotides were identified by paper chromatography (for R_P values see Table).

The calcium salt of CDP-ribose was converted into the lithium salt by passage of its solution through a column of Dowex-50 (lithium form) resin. Some lithium chloride was removed from the freeze-dried product by extraction with acetone, and further purification was achieved by precipitation twice from a small quantity of water by addition of acetone. *CDP-ribose* (48 mg.) was homogeneous on paper chromatography and gave positive reactions on paper for phosphate, glycoside, and reducing sugar (Found, in sample dried at 30° for 36 hr. *in vacuo*: P, 11·6%; ratio, cytidine : P : reducing pentose,[14] 0·98 : 2·0 : 1·01. $C_{14}H_{21}O_{15}N_3P_2Li_2$ requires P, 11·4%; ratio as above 1 : 2 : 1).

	R_{CMP} *	Yield (%) †		R_{CMP} *	Yield (%) †
Cytidine-5′ phosphate	1·0	33	P^1P^2-Diribose 5-pyrophosphate ...	0·65	
P^1P^2-Dicytidine-5′ pyrophosphate	0·35	52	CDP-ribose	0·5	13
Ribose 5-phosphate	1·25		Unidentified phosphate	2·41	

* The value R_{CMP} represents the ratio, distance travelled by compound : distance travelled by cytidine-5′ phosphate, in the solvent system alcohol–ammonium acetate solution (pH 3·8) (75 : 30).[15]

† Yields are calculated on the amount of cytidine-5′ phosphate taken. The symmetrical pyrophosphates used above were prepared on a small scale by the action of dicyclohexylcarbodi-imide on the monophosphates. The unidentified product, R_{CMP} 2·41, is presumably a ribose phosphate derivative, since it is formed from ribose 5-phosphate and the carbodi-imide in the absence of cytidine derivatives.

A small sample of CDP-ribose was heated in 0·1N-hydrochloric acid for 1 hr. at 100°. The products, identified by paper chromatography, were cytidine-5′ phosphate and ribose 5-phosphate.

[13] Pontis and Blumsom, *Biochim. Biophys. Acta*, 1958, **27**, 618.
[14] Mejbaum, *Z. physiol. Chem.*, 1939, **258**, 117.
[15] Paladini and Leloir, *Biochem. J.*, 1952, **51**, 456.

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Stability of CDP-ribitol towards Acid.—A sample of natural CDP-ribitol was purified (free from cytidine-5′ phosphate) by paper chromatography in the alcohol–ammonium acetate (pH 3·8) solvent system. The appropriate area was cut out of the paper and washed with alcohol to remove salt, and the nucleotide eluted with water. Aliquot parts (10 μ mole) in hydrochloric acid (1 ml.) at pH 2, 3, and 4 were kept at room temperature for 18 hr. After adjustment to pH 7 with ammonia and concentration *in vacuo*, products were determined by further chromatography on paper. Amounts of nucleotides were determined spectrophotometrically. Hydrolyses (%) were 0 at pH 4, 2·5 at pH 3, and 19·0 at pH 2.

Reduction of CDP-ribose to CDP-ribitol.—To a solution of the lithium salt (10 mg.) of CDP-ribose in a glycine–sodium hydroxide buffer (pH 8·5) was added, with stirring, fresh sodium borohydride (7 mg.), the temperature being kept at 3°. After 1·25 hr. reducing power had been destroyed (Fehling's solution, aniline phthalate, benzidine). After 1·5 hr., when the pH had risen to 9·2, excess of borohydride was destroyed and the pH adjusted to 3·8 by addition of 2N-acetic acid. Well-washed Norit A charcoal (300 mg.) was added and the mixture was stirred for 3 hr., whereupon the extinction at 280 mμ of the supernatant layer had fallen below 0·05. The charcoal, in the form of a small column, was washed with dilute acetic acid solution (pH 3·8) (1 l.), then water (1 l.), and the nucleotide was eluted with alcohol–water–N-ammonia (50 : 49 : 1) which had been cooled to 0°. Recovery of nucleotides was 80—90%. Paper chromatography showed that the product was largely CDP-ribitol, but it contained about 5% of cytidine-5′ phosphate and a similar amount of the borate complex of CDP-ribitol.

The above material, although purer than most samples of the natural nucleotide, was purified further by paper chromatography in alcohol–ammonium acetate (pH 3·8), elution being effected with water after ammonium acetate had been removed by extraction with alcohol. The nucleotide solution was passed through a small column of Dowex-50 (ammonium form) resin to ensure that it was all in the form of its ammonium salt. Eluate and washings were freeze-dried, and the residue dissolved in water (5 ml.), centrifuged, and freeze-dried. The *ammonium salt* of CDP-ribitol was a light brown very hygroscopic powder (Found: P, 8·5. $C_{14}H_{31}O_{15}N_5P_2,9H_2O$ requires P, 8·6%). The low phosphorus content is consistent with the hygroscopic nature of the material. The molecular weight, based on cytidine content, was 724 ($C_{14}H_{31}O_{15}N_5P_2,9H_2O$ requires *M*, 723). The ratio cytidine : P was 1·01 : 2·0. CDP-ribitol requires 1 : 2. The nucleotide consumed 4·1 moles of sodium periodate per mole of cytidine.[16] CDP-ribitol requires 4·0.

Hydrolysis with ammonia and snake venom, and paper chromatography, were carried out by methods described previously.[4] In all respects synthetic and natural nucleotides were indistinguishable.

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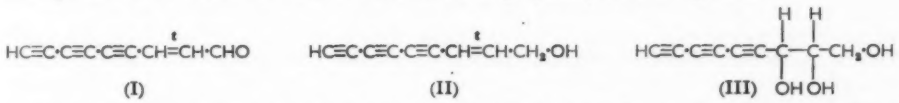
[16] Dixon and Lipkin, *Analyt. Chem.*, 1954, **26**, 1092.

438. *Chemistry of the Higher Fungi. Part IX.* Polyacetylenic Metabolites from* Coprinus quadrifidus.

By E. R. H. Jones and J. S. Stephenson.

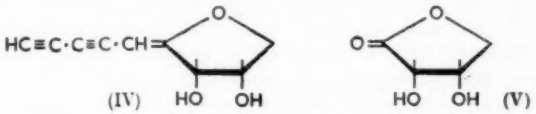
Seven polyacetylenic compounds have been isolated from the culture medium of *Coprinus quadrifidus*. The structures and stereochemistry of four of these products, C_9 compounds (I, II, III, and VIII), have been elucidated.

A brief examination of the antibiotics produced by the Basidiomycete *C. quadrifidus* in stirred, aerated culture has been reported by Doery, Gardner, Burton, and Abraham.[1] They obtained evidence for the presence of several moderately active but toxic substances and, since those that were purified were unstable in the crystalline state, the study was discontinued. Our interest in these products was stimulated by this instability and by the ultraviolet absorption spectra quoted for two fractions obtained from the mixture. Both the light sensitivity of the crystalline materials and the spacing of the sharp maxima of the spectra at *ca.* 2100 cm.$^{-1}$ are characteristic of polyacetylenic compounds.[2]



(I) (II) (III)

The fungus was grown in surface culture and the mixture of compounds in the medium was separated into two main groups by continuous extraction, first with light petroleum (b. p. 30—40°) and subsequently with ether. The less polar fraction was resolved either by chromatography on alumina or by counter-current distribution between hexane and water. Four compounds were thus isolated which, in order of increasing polarity were (*a*) the aldehyde (I), exhibiting the ultraviolet absorption of a carbonyl-ene-triyne chromophore, (*b*) the alcohol (II) (ene-triyne chromophore), (*c*) a compound with maxima at



3095, 2910, 2735, and 2585 Å, and (*d*) another with absorption maxima at 3510, 3280, 3050, 2900, 2610, and 2480 Å. The last compound was at first thought to be the hydroxy-aldehyde (IX) corresponding to the diol (VIII; see below) but when this was obtained by oxidation of the diol with manganese dioxide, its ultraviolet absorption maxima were found to be slightly differently located from those of the natural material. The most likely formula for this compound is the isomeric hydroxy-aldehyde structure (X). No further investigation of materials (*c*) and (*d*) has been possible as only minute quantities were isolated.

The major constituent of the less polar fraction, the alcohol (II), was present in a typical culture medium in a concentration of *ca.* 2 mg./l. It formed unstable colourless crystals from light petroleum at −70°; its lability and its reaction with alcoholic silver nitrate indicated a free ethynyl group. The infrared spectrum confirmed this and established the presence of a hydroxyl group and a *trans*-disubstituted double bond in the molecule. Since catalytic reduction gave nonan-1-ol, structure (II) was established unequivocally.

The substance containing the carbonyl-ene-triyne chromophore, was present mainly

* Part VIII, Bu'Lock, Jones, and Turner, *J.*, 1957, 1607.

[1] Doery, Gardner, Burton, and Abraham, *Antibiotics and Chemotherapy*, 1951, **1**, 409.

[2] Jones, Whiting, Armitage Cook, and Entwistle, *Nature*, 1951, **168**, 900; Bohlmann, *Chem. Ber.*, 1951, **84**, 545, 785.

in the early stages of growth and was available only in very small amounts. Some 10 mg. of material were eventually accumulated during numerous isolations of the other constituents and, after the determination of the structure of the alcohol (II), its investigation was considerably simplified. The compound was purified by chromatography followed by crystallisation at −30°. The pale yellow crystals thus obtained were extremely unstable; at 35° in daylight they were converted almost instantaneously into a bright purple, insoluble polymer. The infrared spectrum showed the molecule to contain a free ethynyl group, an aldehyde group, and a *trans*-disubstituted double bond (a strong band at 1110 cm.$^{-1}$ is regarded as characteristic of an aldehyde grouping in such an environment [3]). The ultraviolet spectrum was compatible with structure (I) and final confirmation was obtained by preparation of the aldehyde by oxidation of the alcohol (II) with manganese dioxide.

$CH_3{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CMe{\cdot}OMe$ (VI)

$CH_3{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}C{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_3$ (VII)

$HO{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH$ (VIII)

$HO{\cdot}CH_2C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CHO$ (IX)

$CHO{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH$ (X)

$H{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}CH{-}CH{\cdot}CH_2{\cdot}OH$ (XI)

The more polar material in the ether extract was shown to consist of at least three polyacetylenic compounds, by counter-current distribution between ether and M/15-phosphate buffer [pH 5·9; used because of the tendency of the triyne-triol to isomerise under mildly basic conditions (see below)]. The major polyacetylene produced by *C. quadrifidus* is the triyne-triol (III). It is present in the culture medium to the extent of *ca.* 50 mg./l. and when pure could be stored for considerable periods at −30° in darkness without appreciable decomposition. Exposure to daylight at 20° caused rapid polymerisation in the crystal lattice (virtually complete in *ca.* 30 min.) whilst when heated quickly to *ca.* 80° the material exploded. Its instability suggested the presence of a free ethynyl group (confirmed with alcoholic silver nitrate), but its infrared spectrum in solution could not be determined owing to the insolubility of the triol in suitable solvents. Hydrogenation (6·0 mol. of hydrogen absorbed) gave a nonane-1 : 2 : 3-triol, characterised as its tribenzoate, and further identified by periodate oxidation (2·05 mol. consumed) to heptaldehyde. The only structure for a triyne-triol compatible with the above evidence is (III).

Advantage was taken of a transformation of the triol (III) which occurred under alkaline conditions to determine the absolute configuration of the asymmetric centres. The product of this reaction exhibited ultraviolet light absorption (see Table) characteristic of a diyne-enol ether (*e.g.*, VI).[4] On the basis of this correlation and by analogy with similar rearrangements of pent-4-yn-1-ol [5] and of deca-4 : 6 : 8-triyne-1 : 2-diol, the latter yielding (VII),[6] a cyclic enol ether structure (IV) was indicated for the product; this was supported by infrared absorption observations. The initial configuration of the two hydroxyl groups is retained in (IV) and this on ozonolysis gave L-erythronolactone (V). The full structure of the triol is thus given by the Fischer projection (III) [(2*D* : 3*D*)-nona-4 : 6 : 8-triyne-1 : 2 : 3-triol on Linstead's convention (see *J.*, 1950, 3333)].

The frequency (1755 cm.$^{-1}$) of the carbonyl band in the infrared spectrum of L-erythronolactone presents a good example of the bathochromic effect of hydrogen bonding. The band appears at 1800 cm.$^{-1}$ in the dibenzoate, a rather high value, possibly due to strain

[3] Personal communication from Dr. M. C. Whiting.
[4] Bohlmann and Viehe, *Chem. Ber.*, 1955, **88**, 1017.
[5] Paul and Tchelitcheff, *Compt. rend.*, 1950, **230**, 1872.
[6] Jones, Turner, and Whiting, unpublished results.

induced in the five-membered ring by two bulky *cis*-substituents or to the close proximity of three carbonyl groups as in glycerol triesters.[7]

The most polar compound present in the poly-yne mixture showed typical ene-diyne absorption maxima at 2805, 2650, 2510, 2385, 2275, and 2100 Å. Little work has been possible on this compound, but it seems likely that it is not simply the partially reduced derivative of the main component, the triyne-triol, since the product obtained on catalytic reduction appears to differ from the nonane-1 : 2 : 3-triol obtained from (III).

The least polar compound of this group is present in small quantities and its ultraviolet spectrum (ene-triyne chromophore) shows maxima similar to those of the ene-triynol (II) but displaced to somewhat longer wavelengths. This spectrum and the considerable stability of the compound suggested the absence of a free ethynyl grouping. This was confirmed by the infrared spectral data which also showed the double bond to have a *trans*-configuration. Catalytic hydrogenation of the compound and subsequent oxidation afforded sebacic acid together with some decanoic acid (formed by hydrogenolysis of a hydroxyl group). The compound was therefore formulated as the diol (VIII) and this was confirmed synthetically by the coupling [8] of penta-2 : 4-diyn-1-ol and *trans*-5-bromo-pent-2-en-4-yn-1-ol.

The variation in oxidation states of the 9-carbon atom chain present in compounds (I), (II), and (III) is of interest and may be significant in relation to the biogenetic processes occurring with *C. quadrifidus*. During preliminary growth studies it was observed that the ene-triyn-ol (II) was accompanied by significant quantities of the aldehyde (I) only in the very early stages of growth. On the other hand the concentration of the alcohol (II) reached a maximum after approximately 30 days, suggesting that it may be formed by reduction of the aldehyde (I). A plausible route to the triol (III) would be by *trans*-hydroxylation of the *trans*-double bond in (II), probably *via* an epoxide. Some evidence is available, which it is hoped to augment in due course, that the constituent (*c*) of the less-polar fraction (p. 2197) is the *trans*-epoxide (XI).

Ultraviolet spectra.

(I)	$\lambda_{max.}$	2105	2200 †	2280	2400	2570	2710	2870	3060	3270	
	$10^{-3}\,\varepsilon$	20·2		60·5	86·5	3·05	6·55	13·1	17·1	12·3	
(II)	$\lambda_{max.}$ *			2330	2430	2550		2830	3000	3200	3430
	$10^{-3}\,\varepsilon$			28·5	47·5	73·5		9·1	19·4	29·5	23·0
(III)	$\lambda_{max.}$	2080				2540	2695	2865	3050		
	$10^{-3}\,\varepsilon$	122				0·16	0·22	0·25	0·17		
(IV)	$\lambda_{max.}$		2160	2240			2650 †	2785	2930		
	$10^{-3}\,\varepsilon$		18·1	23·4			12·5	17·5	14·3		
(VII)	$\lambda_{max.}$		2170	2240			2650	2780	2935		
	$10^{-3}\,\varepsilon$		22·5	30·0			13·0	13·5	15·0		
(VI)	$\lambda_{max.}$			2220			2645	2770	2950		
	$10^{-3}\,\varepsilon$			27·4			10·3	15·0	12·0		
(VIII)	$\lambda_{max.}$	2050	2120	2310	2435	2590	2790	2905	3095	3305	
	$10^{-3}\,\varepsilon$	37·5	37·0	71·5	91·5	3·55	6·4	11·2	13·2	8·1	
(IX)	$\lambda_{max.}$				2470	2595	2875	3050	3250	3485	
	$10^{-3}\,\varepsilon$				46·5	69·5	8·2	16·8	24·8	19·5	

* In hexane. † Shoulder.

The isolation of these C_9 compounds (I, II, and III) makes possible a generalisation on a relation between chain-length and structure of the fungal polyacetylenes. Up to the present all the compounds containing an odd number of carbon atoms also have a free ethynyl grouping; none of those of even chain length contains such a system. So far, seven odd-numbered compounds have been described (3 in this paper, biformin,[9] nemotin and nemotinic acid,[10] and the C_{13} mycomycin [11]) but several more examples known to us will be reported in a subsequent publication.

[7] Shreve, Heether, Knight, and Swern, *Analyt. Chem.*, 1950, **22**, 1498.
[8] Chodkiewicz, *Ann. Chim.* (*France*), 1957, **2**, 819.
[9] Anchel and Cohen, *J. Biol. Chem.*, 1954, **208**, 319.
[10] Bu'Lock, Jones, and Leeming, *J.*, 1956, 3767.
[11] Celmer and Solomons, *J. Amer. Chem. Soc.*, 1952, **74**, 1870.

This generalisation and the occurrence together as metabolic products of *C. quadrifidus* of C_{10} derivatives (VIII) and (X) with oxygen functions at both ends, along with the C_9 compounds (I), (II), and (III) suggest that the terminal methyl group of polyacetylenic derivatives of even chain length is removed by ω-oxidation followed by decarboxylation. The alcohol (II) might arise thus:

$$CH_3{\cdot}[C{\equiv}C]_3{\cdot}CH{=}CH{\cdot}CO_2H \longrightarrow HC{\equiv}C{\cdot}[C{\equiv}C]_3{\cdot}CH{=}CH{\cdot}CH_2{\cdot}OH$$

by consecutive oxidation, decarboxylation and reduction steps. Some evidence has already been obtained of the existence of an enzyme system in cell-free extracts of *C. quadrifidus* capable of decarboxylating a triyne-acid.

Bu'Lock and Gregory [12] have provided a clear demonstration that the carbon chain of the C_{11} nemotinic acid is built up from acetate units. Working with [1-^{14}C]acetate they found that the radioactivity was confined to the odd-numbered carbon atoms and suggested that the twelfth carbon atom (which remains in the accompanying odyssic acid) is eliminated by oxidation followed by decarboxylation. In support of this they draw attention to the apparent interconvertibility of C_{10} compounds with CH_3, $CH_2{\cdot}OH$, and CO_2H terminal groups in cultures of *Polyporus anthracophilus*.[13] It appears that the enzyme system responsible for decarboxylation is not present in this fungus.

Experimental

Ultraviolet absorption spectra (cf. Table) were measured for ethanol solutions, unless otherwise stated (chromatographic and distribution fractions were examined directly), on a Cary Recording Spectrophotometer Model 14 M. Infrared absorption spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer, and m. p.s (corrected) determined on a Kofler block. Alumina for chromatography was Peter Spence grade " H," deactivated by treatment with 5% of 10% acetic acid. Light petroleum refers to a fraction with b. p. 60—80°. Evaporations were done under reduced pressure in nitrogen. Crystallisations of poly-ynes were carried out in a cold room (−9°) in red light.

The culture of *C. quadrifidus* was obtained from the Type Culture Collection, Baarn (Netherlands). The fungus was grown as surface cultures on a 5% solution of malt extract, and the culture medium was decanted and extracted after 30 days' growth at 24°. Subsequent replacement of the medium with a 4% solution of glucose [14] or a 4% glucose solution containing sodium acetate (0·2M) resulted in an enhanced rate of poly-yne production, comparable concentrations to those obtained during the initial growth period being produced after 7 to 14 days' growth.

The Less Polar Poly-yne Fractions.—In a typical experiment 36 l. of the culture medium (12 l. batches) were continuously extracted with light petroleum (b. p. 30—40°). The extract was evaporated to 160 c.c. and placed in the first 4 tubes of a 50 plate Craig countercurrent apparatus (volumes of upper and lower phases, 40 c.c.) and distributed between light petroleum and water. After 70 transfers the alcohol (II) appeared in tubes 28—50 and in fractions 9—20 removed from the apparatus. The less polar aldehyde (I) appeared in fractions 1—12, whilst the two polar fractions, one with ultraviolet absorption bands at 3510, 3280, 3050, 2900, 2610, and 2485 Å and the other showing maxima at 3095, 2900, 2735, and 2585 Å, were found in tubes 1—14 and tubes 14—22 respectively. The last material was adsorbed from benzene (10 c.c.) on alumina (50 g.). It was eluted with benzene–ether (19 : 1; 50 c.c.) and exhibited $\lambda_{max.}$ 2095, 2585, 2735, 2950, and 3095 Å and $\nu_{max.}$ 3580 (O–H), 3300 (≡C–H), 1087, 1065 (C–O), 904, 874, 844, and 755 cm.$^{-1}$. The partition coefficient between light petroleum–benzene (3 : 1) and water at 17° is 1·0. The ratio of the intensity of the absorption band at 2095 to that at 3095 Å is 120 : 1, much lower than the corresponding ratio, 717 : 1, observed in the case of the triyne-triol (III).

trans-*Non*-2-*ene*-4 : 6 : 8-*triyn*-1-*ol* (II).—The fractions (14—20) and contents of tubes (32—50) rich in material with ene-triyne absorption were combined; the aqueous phase was

[12] Bu'Lock and Gregory, *Biochem. J.*, 1959, in the press. We are indebted to Dr. J. D. Bu'Lock for keeping us informed about the progress of these closely related studies.
[13] Bu'Lock, Jones, and Turner, *J.*, 1957, 1607.
[14] Bu'Lock and Leadbeater, *Biochem. J.*, 1956, **62**, 476.

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extracted with ether. The ether and light petroleum solutions were evaporated to 50 c.c., and, on cooling to −70°, trans-*non*-2-*ene*-4 : 6 : 8-*triyn*-1-*ol* (II; 70 mg.) separated as colourless needles. The material was then recrystallised from hexane at −70° and a sample dried at 10^{-2} mm. for 30 min. at −9°. The ultraviolet extinction coefficients of the ene-triyne alcohol (see Table) were then obtained after direct and rapid weighing on a torsion balance. In light at room temperature the poly-yne (II) was first converted into a purple polymer which rapidly became black (*ca.* 3 min.) and totally insoluble in the usual organic solvents. The alcohol had $\nu_{max.}$ (in CS_2) 3600 (O–H), 3290 (≡C–H), 1090 and 1027 (C–O) and 943 $cm.^{-1}$ (=C–H); (in CCl_4): 2190 (–C≡C–) and 2040 $cm.^{-1}$ (–C≡C–H). The distribution coefficient at 17° between hexane and water was 1·35.

Hydrogenation of trans-*Non*-2-*ene*-4 : 6 : 8-*triyn*-1-*ol* (II).—A solution of the alcohol (II) (48·0 mg.) in ethanol (30 c.c.) was hydrogenated over pre-reduced platinic oxide (56·7 mg.) [54 c.c. (N.T.P.) hydrogen absorbed ≡6·5 mol.], to give nonan-1-ol (41·5 mg.) shown to be homogeneous and identified by vapour-phase chromatography. (*a*) By use of a column at 160°, length 300 cm., packed with silicone rubber E301 (20 parts) on firebrick (80 parts; 30—40 mesh), the retention time of the only fraction was 28 min. (octan-1-ol, 17 min.; nonan-1-ol, 27 min.; decan-1-ol, 42 min.). (*b*) On use of a column at 180°, length 483 cm., packed with silicone oil MS 550 (20 parts) on firebrick (80 parts; 50—90 mesh) the retention time was 44·5 min. (nonan-1-ol, 44·5 min.).

Hydrogenation of the alcohol (II) (81·4 mg.), treatment of the product with *p*-phenylazobenzoyl chloride in pyridine, and crystallisation from ethanol gave *nonyl* p-*phenylazobenzoate* (167 mg.), laths, m. p. 54—55° (Found: C, 75·2; H, 8·0; N, 7·7. $C_{22}H_{28}O_2N_2$ requires C, 74·95; H, 8·0; N, 7·95%). The m. p. was undepressed on admixture with a specimen made from authentic alcohol. *Decyl* p-*phenylazobenzoate* (laths from ethanol) has m. p. 59·5—60° (Found: C, 75·1; H, 8·3; N, 7·5. $C_{23}H_{30}O_2N_2$ requires C, 75·35; H, 8·25; N, 7·65%). A mixed m. p. with nonyl derivative was 52—59°.

trans-*Non*-2-*ene*-4 : 6 : 8-*triyn*-1-*al* (I).—Material obtained during numerous isolations of the ene-triyne (II) was combined and adsorbed from light petroleum on alumina (100 g.). Elution with this solvent and careful evaporation at 10 mm. at −9° in red light gave trans-*non*-2-*ene*-4 : 6 : 8-*triyn*-1-*al* (I) which was further purified by crystallisation from light petroleum (b. p. 30—40°) at −30°. The crystalline compound (6 mg.; estimated spectroscopically) was dried at −9°/10^{-2} mm. for 10 min. A sample was then weighed rapidly (torsion balance) for the determination of ultraviolet absorption data (see Table). $\nu_{max.}$ (in CS_2) were at 3290 (≡C–H), 2740 (OC–H), 1693 (C=O), 1110 (C–CHO), and 950 $cm.^{-1}$ (=C–H).

Manganese Dioxide Oxidation of trans-*Non*-2-*ene*-4 : 6 : 8-*triyn*-1-*ol* (II).—A solution of the alcohol (II) (85 mg.) in methylene dichloride (120 c.c.) was shaken with active manganese dioxide (1·2 g.) for 15 hr. at 20°. The solvent was then removed at −9°/10^{-2} mm., and the residual material adsorbed from light petroleum on alumina (40 g.). Elution with light petroleum (50 c.c.) afforded a fraction (4 mg.), having ultraviolet and infrared absorption spectra identical with those of the natural aldehyde (I).

The More Polar Poly-yne Fractions.—The culture medium from 100 flasks (75 l.) was continuously extracted (in 10 l. batches) with ether for 72 hr., the ethereal solution was evaporated to *ca.* 2 l., M/15-phosphate buffer (150 c.c.) was then added, and evaporation continued until *ca.* 500 c.c. of ether remained. Benzene (1 l.) was then added to ensure that poly-acetylenic compounds with low water-solubility would remain in solution, and the residual ether was removed. The aqueous phase, containing the bulk of the polar poly-acetylenes, was separated and placed in the first four tubes of a 50-plate Craig counter-current apparatus (volumes of upper and lower phases, 40 c.c.) and distributed between ether and M/15-phosphate buffer (pH 5·9). After 50 transfers the most polar compound, that with ene-diyne absorption, remained in tubes 1—9 whilst the main component, the triol (III), appeared in tubes 19—35. A small amount of material with the ultraviolet absorption characteristics of an ene-triyne was in the tubes 43—48 whilst non-polar material moved with the solvent front.

(2D : 3D)-*Nona*-4 : 6 : 8-*triyne*-1 : 2 : 3-*triol* (III).—The ethereal solution (2·5 l.) from tubes 19—35 was stored at −9°. To ensure homogeneity of the product, portions of this solution (800 c.c.) were evaporated to 40 c.c. and redistributed in the same solvent system. After 130 transfers the triol (III) appeared in fractions 32—62, and ultraviolet spectral measurements showed that it was almost pure. These fractions were combined and evaporated to 30 c.c., hexane was added dropwise to the cooled (−9°) solution, the *triyne-triol* (III) (1·15 g.) separating

as needles (decomp. *ca.* 40°). The original 75 l. of culture fluid must have contained a minimum of 3·5 g. of triol.

Reproducible ultraviolet absorption data (see Table) were obtained as before. Solutions were then standardised by means of their absorption intensities. $[\alpha]_D$ was +6° (*c* 0·82) in ethanol. The partition coefficient between ether and water at 21° was 1·2. With alcoholic silver nitrate the triol gave a colourless precipitate which darkened rapidly on exposure to light. The acid liberated was detected by the Methylene Blue–Methyl Red indicator [15] but reproducible titres were not obtained.

(2D : 3D)-*Nonane*-1 : 2 : 3-*triol*.—Hydrogenation of the triol (III) (138 mg.) in ethyl acetate (50 c.c.) over pre-reduced platinic oxide [110 c.c. (N.T.P.) hydrogen absorbed ≡6 mol.], and crystallisation of the product from ether gave the *triol* (110 mg.), m. p. 103—104°, $[\alpha]_D$ +15° (*c* 1·0) in ethanol, $\nu_{max.}$ (in Nujol) 3300 (v. broad) (O–H) and 1070 cm.$^{-1}$ (C–O) (Found: C, 61·2; H, 11·5. $C_9H_{20}O_3$ requires C, 61·3; H, 11·4%).

Benzoylation of the triol (80 mg.) with pyridine–benzoyl chloride gave the *tribenzoate* (160 mg.), needles (from light petroleum), m. p. 94—95°, $[\alpha]_D$ −22° (*c* 0·8 in chloroform) (Found: C, 74·0; H, 6·4. $C_{30}H_{32}O_6$ requires C, 73·8; H, 6·6%), $\nu_{max.}$ (in CS_2) 2930 (C–H), 1735 (C=O), 1605, 1455, 1250, 1105, and 708 cm.$^{-1}$.

Periodate Oxidation of (2D : 3D)-*Nonane*-1 : 2 : 3-*triol*.—A solution of the triol (22·1 mg.) in water (25 c.c.) was used in a quantitative periodate estimation 2·05 mol. consumed). Heptaldehyde was isolated by ether-extraction and gave a 2 : 4-dinitrophenylhydrazone (25 mg.), m. p. 105—106°, undepressed by admixture with an authentic specimen but depressed to 94—102° and 90—98° by octaldehyde and hexaldehyde 2 : 4-dinitrophenylhydrazones respectively.

(3L : 4L)-*Tetrahydro*-2-(*penta*-2 : 4-*diynylidene*)*furan*-3 : 4-*diol* (IV).—A solution of the triol (III) (320 mg.) in water (225 c.c.) was treated with N-sodium hydroxide solution (25 c.c.) and kept in darkness at 20° under nitrogen for 5 hr. The resulting solution was extracted continuously with ether for 15 hr. and the extract dried, evaporated to 20 c.c., and cooled to −9°. Careful addition of hexane afforded crystals (300 mg.); two recrystallisations from ether–hexane at −9° gave the pure *diol* (IV), decomp. 94°, $[\alpha]_D$ −165° (*c* 0·5 in ethanol) (Found: C, 65·7 H, 4·8. $C_9H_8O_3$ requires C, 65·85; H, 4·9%, $\nu_{max.}$ (in CCl_4) 3580 (O–H), 3300 (≡C–H), 2200 (C≡C), 1655 (=C–O), 1125, 1035, 975, and 874 cm.$^{-1}$ (for ultraviolet absorption data (see Table).

L-*Erythronolactone* (V).—A solution of (V) (850 mg.) in ethyl acetate (250 c.c.) at −35° was treated with ozonised oxygen (11 l./min.; 2%) until a permanent blue colour appeared. The mixture was then evaporated to 20 c.c. at 20° and 0·05N-hydrochloric acid (100 c.c.) was added. The remaining ethyl acetate was then removed and the solution left at 20° for 12 hr. Evaporation at 10^{-3} afforded a gum which was distilled at 120°/0·1 mm. The distillate (305 mg.) was crystallised from ethyl acetate, to give L-erythronolactone (V) (160 mg.), m. p. 100—102°, $[\alpha]_D$ +73° (*c* 0·85 in water) (Jelinek and Upson [16] give m. p. 102°, $[\alpha]_D$ +72·5°), $\nu_{max.}$ (in Nujol) 3450 (O–H), 3280 (hydrogen bonded O–H), and 1755 cm.$^{-1}$ (γ-lactone C=O) + many in 1200—800 cm.$^{-1}$ region. Benzoylation gave the dibenzoate, m. p. 108·5—109·5°, $[\alpha]_D$ +182° (*c* 1·0 in chloroform) (Jelinek *et al.*[16] give m. p. 110—111°, $[\alpha]_D$ +176°) (Found: C, 65·9; H, 4·35. Calc. for $C_{18}H_{14}O_6$: C, 66·25; H, 4·3%), $\nu_{max.}$ (in Nujol) 1800 (γ-lactone C=O) and 1725 cm.$^{-1}$ (benzoate C=O), (in CS_2) 1815, 1739 cm.$^{-1}$.

trans-*Dec*-2-*ene*-4 : 6 : 8-*triyne*-1 : 10-*diol* (VIII).—To obtain significant amounts of this compound a different procedure to that used in the isolation of the triol (III) was adopted. After continuous extraction with light petroleum (b. p. 30—40°) to remove the less polar constituents, the culture medium (50 l.) was continuously extracted with ether. The polyacetylenes in the ethereal extract were transferred to a benzene–water system (80 c.c. of each phase): a considerable amount of the triol (III) was precipitated and thus removed. The solution was then placed in the first two tubes of a 50-plate counter-current apparatus. After 53 transfers the contents of the tubes 26—40 were combined, and the aqueous layer was separated and extracted with ether. The polyacetylene present in the benzene layers and the ethereal extract was adsorbed from benzene (100 c.c.) on alumina (130 g.). Benzene–ether (1 : 1; 200 c.c.) eluted the *diol* (VIII) (16 mg.) which crystallised as colourless needles (from chloroform), decomp. 138° (Found: C, 75·5; H, 5·0. $C_{10}H_8O_2$ requires C, 75·0; H, 5·0%), $\nu_{max.}$ (in Nujol) 3200 (O–H), 1080 and 1013 (C–O), and 944 cm.$^{-1}$ (=C–H) (for ultraviolet absorption data see Table), partition coefficient 1·12 between benzene and water at 21°.

[15] Eglinton and Whiting, *J.*, 1953, 3055.
[16] Jelinek and Upson, *J. Amer. Chem. Soc.*, 1938, **60**, 355.

Hydrogenation of trans-*Dec*-2-*ene*-4 : 6 : 8-*triyne*-1 : 10-*diol* (VIII).—A solution of the diol (VIII) (47·3 mg.) in ethanol (200 c.c.) was hydrogenated over 5% palladised charcoal (37·8 mg.) [44 c.c. of hydrogen (N.T.P.) absorbed ≡6·7 mol.]. The product was sublimed at 80°/3 × 10^{-2} mm. to give decanoic acid (10 mg., formed by hydrogenolysis of a hydroxyl group) characterised as its anilide (m. p. 67°). The residue after sublimation was sebacic acid (35 mg.), m. p. and mixed m. p. 130—134° (from ethyl acetate).

Synthesis of Diol (VIII).—A solution of *trans*-5-bromopent-2-en-4-yn-1-ol (735 mg.) in methanol (5 c.c.) was added under nitrogen during 15 min. to a stirred solution of penta-2 : 4-diyn-1-ol (350 mg.) and cuprous chloride (30 mg.) in 33% aqueous ethylamine (10 c.c.), at 25—30°. Hydroxylamine hydrochloride was added in small portions as the reaction proceeded to ensure that the copper remained in the reduced form. After the addition was complete stirring was continued for a further 5 min., then aqueous potassium cyanide solution was added, and the mixture extracted with ether. The yield of the diol (VIII) as estimated spectroscopically was 300 mg.

The material (150 mg.) was distributed between benzene and water (the amount treated being limited by the fairly low solubility of the compound). Thus purified, the diol (100 mg.) crystallised from chloroform (Found: C, 74·9; H, 5·4. Calc. for $C_{10}H_8O_2$: C, 75·0; H, 5·0%) and was identical with the natural material.

trans-*Dec*-2-*ene*-4 : 6 : 8-*triyn*-10-*ol*-1-*al* (IX).—A solution of the diol (VIII) (60 mg.) in methylene dichloride (250 c.c.) was shaken at 20° for 24 hr. with active manganese dioxide (3·0 g.). The oxidant was then removed and the solvent carefully evaporated under reduced pressure. The residue was adsorbed from benzene (20 c.c.) on alumina (70 g.). Benzene (100 c.c.) eluted a trace of material which must be a dialdehyde. Benzene–ether (19 : 1; 200 c.c.) eluted the *hydroxy-aldehyde* (IX) (24 mg.) and starting material (21 mg.) was recovered by elution with ether. The hydroxy-aldehyde (IX) crystallised from ether–hexane as off-white needles, m. p. *ca.* 90° (decomp.), which slowly became reddish-brown in light (Found: C, 75·55; H, 4·2. $C_{10}H_6O_2$ requires C, 75·95; H, 3·8%), $\nu_{max.}$ (in Nujol) 3350 (O–H), 1665 (C=O), 1095 and 1023 (C–O), and 958 cm.$^{-1}$ (=C–H) (for ultraviolet absorption data see Table).

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439. *Griseofulvin. Part XVI.* Synthesis of Compounds related to Griseofulvin.*

By A. W. DAWKINS and T. P. C. MULHOLLAND.

Racemic spirans related to griseofulvin have been prepared by condensation between coumaranones and dibromoalkanes. The presence of the grisan ring system in griseofulvin has been confirmed by synthesis of 7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3-one, which is shown to be the racemate of the (*l*,*d*)-stereoisomer,† obtained by degrading the (*l*,*d*)-diastereoisomer of griseofulvin.

The synthesis of racemates of some non-spiran oxidation products, and improved preparations of certain dibromoalkanes, are also described.

THE structures (I; R = Cl and H) proposed for griseofulvin [1] and dechlorogriseofulvin [2] respectively were supported by syntheses [3] of several non-spiran degradation products.

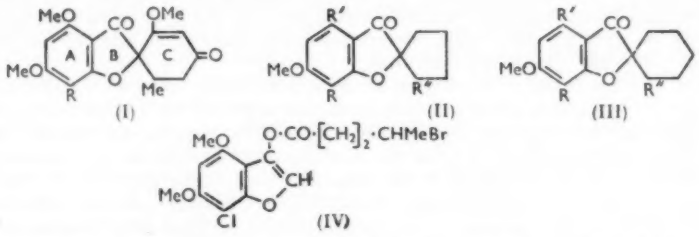
The preparation of further non-spiran degradation products is described in this paper

* Part XV, *J.*, 1959, 1830.

† The prefixes denote the configuration of the two asymmetric centres, the spiran centre preceding. Griseofulvin is defined (Part XIV) as the (*d*,*d*)-stereoisomer; inversion of the spiran centre yields the (*l*,*d*)-diastereoisomer.

[1] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3977.
[2] MacMillan, *J.*, 1953, 1697.
[3] MacMillan, Mulholland, Dawkins, and Ward, *J.*, 1954, 429.

together with the synthesis of a racemate of a spiran degradation product, thus confirming the presence of the grisan ring system in griseofulvin.



Three routes to spirocyclic derivatives of griseofulvin were investigated: (*a*) Condensation of appropriate coumaranones and dibromoalkanes, (*b*) ester syntheses from 2 : 2-disubstituted coumaranones, and (*c*) a modification of the Dean and Robertson synthesis of usnolic acid analogues.[4] The last route is described in the following paper.

(a) *Dibromoalkane Syntheses.*—In this method, briefly reported elsewhere,[5] condensation of suitable dibromoalkanes with coumaran-3-ones in the presence of potassium *tert.*-butoxide (but not ethoxide or methoxide) gave spirans (see Table 1). The yields were low but the method was simple and the starting materials were readily prepared.

TABLE 1.

Coumaranone	Halide	Product
6-Methoxy-	1 : 4-Dibromopentane	II; R = R′ = H, R″ = Me
7-Chloro-4 : 6-dimethoxy-	1 : 4-Dibromobutane	II; R = Cl, R′ = OMe, R″ = H
,, ,,	1 : 5-Dibromopentane	III; R = Cl, R′ = OMe, R″ = H
,, ,,	1 : 5-Dibromohexane	III; R = Cl, R′ = OMe, R″ = Me

The condensation failed with a bromoacyl bromide; γ-bromovaleroyl bromide and 7-chloro-4 : 6-dimethoxycoumaranone gave the coumaronyl ester (IV).

The synthetic racemates (II; R = R′ = H, R″ = Me) and (III; R = Cl, R′ = OMe, R″ = Me) behaved as single racemates. The m. p. of the latter was depressed by mixture with (*d*,*d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan (Product C, m. p. 147—148°) obtained [6] from griseofulvin and the infrared spectra in solution differed; but the m. p. was not depressed on admixture with the (*l*,*d*)-stereoisomer [7] and the infrared spectra were identical. The synthetic product was therefore the racemate of the latter and the presence of the grisan ring system in griseofulvin was confirmed.

It was necessary to develop improved syntheses of 1 : 4-dibromopentane and 1 : 5-dibromohexane since published methods gave low yields, *e.g.*, for the latter [8] only 1%. Fission of heterocyclic compounds gave good results. 1 : 4-Dibromopentane was prepared in 90% yield by treating tetrahydro-2-methylfuran with sodium bromide and concentrated sulphuric acid. 1 : 5-Dibromohexane was prepared in 61% yield by treating 1-benzoyl-2-methylpiperidine with phosphorus tribromide and bromine.[9]

Contrary to Slater and Stephen's findings,[10] methylation of 6-hydroxycoumaranone gave the 6-methoxy-compound.

(b) *Ester Syntheses.*—Although this route did not yield spirocyclic compounds, it led to racemates of several oxidation products of griseofulvin and dechlorogriseofulvin.

Methyl crotonate and 7-chloro-4 : 6-dimethoxycoumaran-3-one gave the ester (V; R = Cl, R′ = H, R″ = Me) which was separated into two racemates, α and β, by

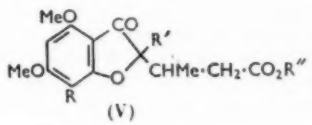
[4] Dean, *Sci. Progr.*, 1952, **40**, 653.
[5] Dawkins and Mulholland, XVIth Internat. Congr. Pure Appl. Chem., Paris, 1957.
[6] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3949.
[7] Dawkins and Mulholland, *J.*, 1959, 1830.
[8] Perkin, *J.*, 1887, **51**, 702.
[9] von Braun, *Ber.*, 1904, **37**, 2915.
[10] Slater and Stephen, *J.*, 1920, **117**, 309.

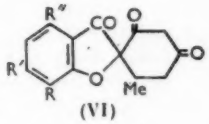
crystallisation. The m. p. (83—86°) of the latter was not depressed on admixture with material of $[\alpha]_D$ −19°, m. p. 96—98°, obtained by degradation of griseofulvin *via* the trione (VI; R = Cl, R′ = R″ = OMe),[11] and the infrared spectra in chloroform solution were identical.

Acidic hydrolysis of either ester gave the same acid (V; R = Cl, R′ = R″ = H) which regenerated a mixture of the esters on methylation. A mixture of the esters was obtained by heating either of the pure esters with potassium carbonate in acetone.

Alkaline hydrolysis of the synthetic acid (V; R = Cl, R′ = R″ = H), like that of the optically active material,[11] gave the phenolic acid (VII), which was shown to be the 6-hydroxy-compound by the infrared spectrum in dilute chloroform solution (C=O, 1701 cm.$^{-1}$).[12]

The acid (V; R = Cl, R′ = R″ = H) with alkaline permanganate gave the hydroxy-acid (V; R = Cl, R′ = OH, R″ = H) whose infrared spectrum in Nujol "mull" was identical with that of material of $[\alpha]_D$ −17° (in acetone) from griseofulvin.[11,13] Dehydration gave the lactone (VIII; R = Cl) which could not be separated into two racemates. Its infrared spectrum in Nujol mull, m. p., and mixed m. p. were identical with those of lactone A.[11]


(V)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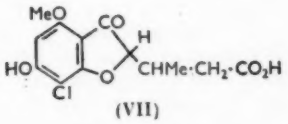
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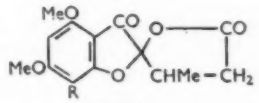
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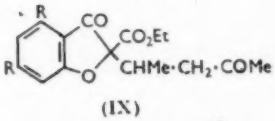
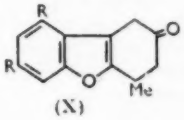
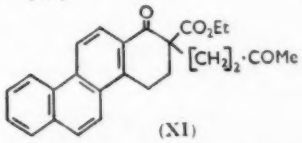

(IX)


(X)


(XI)

In the dechlorogriseofulvin series the synthetic ester (V; R = R′ = H, R″ = Me) was obtained as a mixture of two isomeric forms, probably corresponding to the two racemates (cf. above). Only one form crystallised. Acidic hydrolysis of the mixture of non-crystalline ethyl esters (V; R = R′ = H, R″ = Et) gave a gum consisting essentially of the acid (V; R = R′ = R″ = H) but containing varying amounts of a phenolic impurity which was eliminated during oxidation to the crystalline hydroxy-acid (V; R = R″ = H, R′ = OH). This was less stable than the chlorine-containing analogue and it was not obtained in pure form from dechlorogriseofulvin.[2] The synthetic acid often contained the lactone (VIII; R = H) into which it was converted easily. The lactone was also obtained directly, but in low yield, by oxidation of ethyl 4 : 6-dimethoxy-3-oxocoumaran-2-β-butyric acid (V; R = R′ = H, R″ = Et). The m. p. of the lactone was not depressed on admixture with the lactone prepared from dechlorogriseofulvin, and the infrared spectra were identical.

Attempts to prepare the triones (VI; R = H, R′ = R″ = OMe; and R = R′ = R″ = H) from the available 3-oxocoumaran-2-carboxylates[3] failed. In particular the esters (IX; R = H, and R = OMe) could not be cyclised to spirans although they gave the corresponding dibenzofurans (X; R = H and R = OMe) when heated with aqueous

[11] Grove, Ismay, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3958.
[12] Duncanson, Grove, MacMillan, and Mulholland, *J.*, 1957, 3555.
[13] MacMillan, *J.*, 1959, 1823.

alkali.[3] Under basic conditions a reverse Michael reaction often occurred, giving the oxocoumaran-2-carboxylates, and in acidic media starting material or intractable products resulted. The ester (XI) similarly fails to cyclise to a spiran.[14]

Experimental

M. p.s are corrected. Microanalyses are by Messrs. W. Brown and A. G. Olney. Alumina (B.D.H. or Peter Spence Type H) was (*a*) used without further treatment (pH 10), (*b*) rendered alkali-free [15] and activated at 250°/17 mm. for 3 hr. (pH 4; Grade II), or (*c*) washed with water after treatment with nitric acid and then treated with methanol and activated (pH 7; Grade II). Silica was material of large pore-size (<100 B.S.S.; pH 6·75). Chromatography was carried out in ultraviolet light. Ultraviolet spectra (ethanol solutions) and infrared spectra (Nujol mulls unless stated otherwise) were obtained as described previously.[16] Light petroleum had b. p. 40—60°.

1 : 4-*Dibromopentane*.—A solution of sodium bromide (109 g.) and concentrated sulphuric acid (137 ml.) in water (125 ml.) was kept at 30° during the gradual addition of tetrahydro-2-methylfuran (43 g.). The mixture was boiled for 2 hr. and steam-distilled. The product recovered from the distillate by ether-extraction was fractionally distilled, giving the dibromo-compound (103 g.), b. p. 98—99°/25 mm., n_D^{15} 1·516 (lit., b. p. 104—106°/30 mm.,[17] n_D^{15} 1·515 [18]).

1 : 5-*Dibromohexane*.—(i) Perkin's method,[8] starting from ethyl acetoacetate and 1 : 3-dibromopropane, gave the following yields: ethyl 5 : 6-dihydro-2-methylpyran-3-carboxylate (62%); the corresponding acid (34%); 6-hydroxyhexan-2-one (69%); hexane-1 : 5-diol (50%); and 1 : 5-dibromohexane (b. p. 153—155°/100 mm.) (17%, overall 1·2%). The physical constants agreed with those reported.

(ii) Phosphorus tribromide (182 g.) and then bromine (120 g.) were added in portions to 1-benzoyl-2-methylpiperidine (140 g.; m. p. 46°; lit., m. p. 44—45° [19]) at 0° with shaking. The product was distilled at *ca.* 20 mm. until the distillate became yellow. Phosphoryl bromide was removed by shaking the distillate with ice (500 g.), and the mixture was extracted with light petroleum. The petroleum extract was washed with sodium carbonate, water, and concentrated sulphuric acid until the washings were colourless. Recovery from the petroleum extract and distillation of the residue gave 1 : 5-dibromohexane (103 g.), b. p. 121—124°/23 mm., which darkened in light. The recorded b. p.[20] was 120—122°/20—25 mm. Use of phosphorus pentabromide gave lower yields.

ω-*Chlororesacetophenone*.—Dry hydrogen chloride was passed into a solution of resorcinol (72·0 g.), chloroacetonitrile (48 g.),[21] and zinc chloride (48 g.) in dry ether for 2 hr. at room temperature. After 1 hr., the ketimine hydrochloride was filtered off, washed with ether, and hydrolysed at 70° with water (5 l.) for 1 hr. The product, which separated on cooling, crystallised from toluene, giving the phenol as nearly colourless needles (85 g.), m. p. 132—133 [lit.,[22] m. p. 131° (uncorr.)].

2-*Chloroacetyl*-5-*methoxyphenol*.—(*a*) The above phenol (30 g.) in ether (300 ml.) with ethereal diazomethane gave a precipitate of the monomethyl ether which crystallised from ethanol in needles (31 g.), m. p. 116—117° (lit.,[23] 116°) (Found: C, 53·6; H, 4·6; Cl, 17·8. Calc. for $C_9H_9O_3Cl$: C, 53·9; H, 4·5; Cl, 17·7%).

(*b*) Powdered aluminium chloride (9 g.) was added to 1 : 3-dimethoxybenzene (8·0 g.) and chloroacetyl chloride (6·5 g.) in carbon disulphide (30 ml.). After 1 hr. the solvent was decanted from the red oil, and the latter was treated with ice-cold water (30 ml.) and concentrated hydrochloric acid (20 ml.). The steam-volatile part of the product was recovered in ether, giving the phenol (3·9 g.), m. p. 111—114°, raised to 116—117° by recrystallisation.

[14] Nasipuri, *Chem. and Ind.*, 1956, 795.
[15] Prins and Shoppee, *J.*, 1946, 494.
[16] Mulholland and Ward, *J.*, 1954, 4676.
[17] Grishkewitsch-Trochimowski, *J. Russ. Phys. Chem. Ges.*, 1916, **40**, 916.
[18] Paul, *Ann. Chim.* (*France*), 1932, **18**, 303.
[19] Bunzel, *Ber.*, 1889, **22**, 1053.
[20] Solonina, *Chem. Zentr.*, 1899, I, 25.
[21] Scholl, *Ber.*, 1896, **29**, 2415; Steinkopf, *Ber.*, 1908, **41**, 2541.
[22] Sonn, *Ber.*, 1917, **50**, 1262.
[23] von Auwers and Pohl, *Annalen*, 1914, **405**, 264.

6-*Methoxycoumaran*-3-*one*.—(*a*) A mixture of 6-hydroxycoumaran-3-one (5·0 g.) in benzene (2 l.) and excess of ethereal diazomethane was kept for 18 hr. Recovery of the neutral product gave the coumaranone (4·2 g.), m. p. 123—125°, which crystallised from ethanol in prisms, m. p. 124—125° (lit.,[24] 125°) (Found: C, 65·7; H, 5·0. Calc. for $C_9H_8O_3$: C, 65·85; H, 4·9%), $\nu_{max.}$ 1710 cm.$^{-1}$, $\lambda_{max.}$ 318, 268, 233, 208 mμ (log ε 4·00, 4·12, 4·05, 4·29).

(*b*) 2-Chloroacetyl-5-methoxyphenol (3·0 g.) was heated with sodium acetate (3·0 g.) in ethanol (150 ml.) for 2 hr. Crystallisation of the recovered product gave the coumaranone (2·2 g.), m. p. 124—125°.

6-*Methoxy*-3-*oxocoumaran*-2-spiro-1′-(2′-*methyl*cyclo*pentane*) (II; R = R′ = H, R″ = Me).—A slurry of 6-methoxycoumaran-3-one (0·82 g.) in benzene (50 ml.) was added simultaneously with 1 : 4-dibromopentane (1·15 g.) in benzene (50 ml.) to a stirred suspension of potassium *tert.*-butoxide (1·4 g.) in benzene (50 ml.) boiling under reflux. When addition was complete (30 min.) the mixture was heated under reflux for 3 hr. The cooled, filtered solution was washed with sodium hydroxide solution and water and evaporated and the residue was chromatographed in benzene on alumina (pH 4; 20 × 1 cm.). Elution of the blue fluorescent band with benzene and recovery gave an oil (300 mg.) containing unchanged dibromide. Rechromatography in light petroleum and elution with ether–light petroleum (20 : 1) gave a gum (42 mg.) which crystallised from light petroleum in prisms (36 mg.) of the *spiran*, m. p. 164—167°, raised to 167—168° by sublimation *in vacuo* and recrystallisation from ethanol (Found: C, 72·1; H, 6·9. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%), $\nu_{max.}$ 1712 cm.$^{-1}$; $\lambda_{max.}$ 318, 267, 233, 208 mμ (log ε 4·01, 4·12, 4·05, 4·29).

7-*Chloro*-4 : 6-*dimethoxy*-3-*oxocoumaran*-2-spirocyclo*pentane* (II; R = Cl, R′ = OMe, R″ = H).—The procedure described above was applied to a slurry of 7-chloro-4 : 6-dimethoxycoumaran-3-one [3] (2·29 g.) in benzene (50 ml.), a solution of 1 : 4-dibromobutane (2·16 g.) in benzene (50 ml.) and potassium *tert.*-butoxide (2·8 g.) in benzene (50 ml.). Heating under reflux for 5 hr. and filtration of the cooled suspension gave a yellow filtrate which was extracted with sodium hydroxide solution. Acidification of the alkaline extract gave 3-chloro-2-hydroxy-4 : 6-dimethoxyacetophenone (60 mg.), m. p. 189—191° after crystallisation, identical with authentic material.[13]

The semi-solid product recovered from the neutral fraction was repeatedly extracted with light petroleum. Recovery from the extract gave a solid (400 mg.), m. p. 182—186°. Sublimation at 110°/10^{-4} mm. followed by crystallisation from ethanol gave prisms, m. p. 192—193°, of the *spiran* (Found: C, 59·1; H, 5·4; Cl, 12·2; OMe, 21·4. $C_{14}H_{15}O_4Cl$ requires C, 59·4; H, 5·35; Cl, 12·55; 2OMe, 21·9%), $\nu_{max.}$ 1717 cm.$^{-1}$; $\lambda_{max.}$ 331, 322, 289, 238, 213 mμ (log ε 3·68, 3·69, 4·30, 4·20, 4·37).

Purification of the petroleum-insoluble neutral fraction by chromatography and sublimation gave starting material (1·08 g.), m. p. 212—214°.

7-*Chloro*-4 : 6-*dimethoxygrisan*-3-*one* (III; R = Cl, R′ = OMe, R″ = H).—7-Chloro-4 : 6-dimethoxycoumaran-3-one (2·29 g.) in benzene (50 ml.) was condensed with 1 : 5-dibromopentane (2·31 g.) in benzene (50 ml.) in the presence of potassium *tert.*-butoxide (2·8 g.) in benzene (50 ml.) as described above. Treatment of the residual orange gum with benzene–light petroleum precipitated a solid (120 mg.). Sublimation of this at 130°/10^{-4} mm. and recrystallisation from ethanol gave prisms (70 mg.) of the *grisan*, m. p. 176—177° (Found: C, 60·5; H, 5·9. $C_{15}H_{17}O_4Cl$ requires C, 60·7; H, 5·8%), $\nu_{max.}$ 1715 cm.$^{-1}$.

Unchanged coumaranone (1·20 g.) was recovered from the benzene–petroleum mother-liquor.

7-*Chloro*-4 : 6-*dimethoxy*-2′-*methylgrisan*-3-*one* (III; R = Cl, R′ = OMe, R″ = Me).—7-Chloro-4 : 6-dimethoxycoumaran-3-one (2·90 g.) was condensed with 1 : 5-dibromohexane (2·44 g.) in the presence of potassium *tert.*-butoxide (2·80 g.) as described in the preceding experiments, identical quantities of benzene being used, but when addition was complete the mixture was heated under reflux for 1·5 hr. The cooled, filtered, sodium hydroxide-washed solution was concentrated to *ca.* 5 ml., diluted with light petroleum (5 ml.), and kept at 0°. Prisms (112 mg.) (A), m. p. 142—146°, separated. The gum recovered from the mother-liquor was chromatographed in benzene on alumina (pH 4; 20 × 0·5 cm.).

Elution with benzene removed a yellow non-fluorescent band (i) followed by a blue band (ii). Further elution with benzene–methanol (50 : 1) removed a second blue band (iii). Recovery and purification of fraction (iii) gave starting material (850 mg.), m. p. 200—203°.

[24] Blom and Tambor, *Ber.*, 1905, **38**, 3589.

Fraction (i) gave a gum (40 mg.) which was sublimed (120—130°/10^{-4} mm.) and crystallised from ethanol in prisms, m. p. 146—150° (25 mg.) (B). The gum (340 mg.) recovered from fraction (ii) crystallised from benzene–light petroleum (b. p. 60—80°) in prisms, m. p. 140—147° (295 mg.) (C). Sublimation of the combined products, A, B, and C at 110—120°/10^{-4} mm. followed by crystallisation from ethanol gave the *grisan* as stout needles (405 mg.), m. p. 157—158° (Found: C, 61·8; H, 6·3; Cl, 11·1; OMe, 20·0. $C_{16}H_{19}O_4Cl$ requires C, 61·8; H, 6·1; Cl, 11·5; 2OMe, 20·0%), $\lambda_{max.}$ 331, 322, 289, 238, 212 mμ (log ε 3·67, 3·70, 4·33, 4·20, 4·41). In an attempt to separate an analytically pure specimen into two racemates recrystallisation was repeated 36 times but no change in m. p. or infrared spectrum occurred.

The m. p. of the racemate was not depressed on admixture with the (*l*,*d*)-stereoisomer (*i.e.*, 2*S* : 2′*R*; m. p. 152—153°) obtained by degradation [7] of the (*l*,*d*)-diastereoisomer of griseofulvin, and the infrared spectra in chloroform were identical. The (*d*,*d*)-stereoisomer [6] (*i.e.*, 2*R* : 2′*R*; m. p. 147—148°, " Product C ") obtained from griseofulvin was distinct. The infrared spectrum in chloroform was different and the m. p. was depressed on admixture with the (*l*,*d*)-stereoisomer or the synthetic racemate.

Attempts to obtain the 2′-hydroxy-derivative of the racemate by oxidation with potassium permanganate in acetone–sodium carbonate solution failed.

Attempted Synthesis of 7-Chloro-4 : 6-dimethoxy-6′-methylgrisan-3 : 2′-dione.—A slurry of 7-chloro-4 : 6-dimethoxycoumaran-3-one (11·45 g.) in benzene (200 ml.) was condensed with 1 : 4-dibromopentan-1-one (12·25 g.) in benzene (100 ml.) in the presence of potassium *tert.*-butoxide (14 g.) in benzene (100 ml.) as described above. Working up gave a red filtrate from which an intractable brown tar (6 g.) was removed by extraction with sodium hydroxide solution. Evaporation of the benzene solution gave a gum which was chromatographed on alumina (25 × 1·5 cm.) giving the following bands: (i) eluted by benzene–methanol (100 : 1), a bright blue fluorescent band; and (ii) eluted by benzene–methanol (25 : 1), a broad pale blue band.

Recovery of material from band (i) gave a gum (1·8 g.) which crystallised from ethanol in prisms (1·3 g.), m. p. 124°, of *7-chloro-4 : 6-dimethoxycoumaron-3-yl γ-bromovalerate* (IV) (Found: C, 46·05; H, 4·4; Cl, 8·9; Br, 20·0; OMe, 15·6. $C_{15}H_{16}O_5ClBr$ requires C, 46·05; H, 4·1; Cl, 9·1; Br, 20·4; OMe, 15·85%), $\nu_{max.}$ 1760, 1623, 1609 cm.$^{-1}$; $\lambda_{max.}$ 265, 219 mμ (log ε 4·18, 4·62), unsaturated to permanganate in acetone and darkening in sunlight. Band (ii) gave starting material (8 g.).

Methyl 7-Chloro-4 : 6-dimethoxy-3-oxocoumaran-2-β-butyrate (V; R = Cl, R′ = H, R″ = Me).—7-Chloro-4 : 6-dimethoxycoumaran-3-one (4·2 g.) in dioxan (200 ml.) at 46° was treated with methyl crotonate (2·1 g.) and N-methanolic sodium methoxide (8·0 ml.). After storage at 55—60° for 6 hr. and at room temperature for 2 days, the filtered mixture was treated with acetic acid (5 ml.) and charcoal, filtered, and evaporated *in vacuo*. A solution of the residue in benzene (150 ml.) was washed with water, dried, and chromatographed on alumina (25 × 2·5 cm.). Elution with benzene–methanol (100 : 1) removed a blue fluorescent band. The recovered product was distilled at 170—200°/10^{-4} mm. on to a cold finger and then crystallised from benzene, giving material (A), m. p. 143—150° (1·0 g.). Extraction of material recovered from the mother-liquor with acetone gave a residue (B), m. p. 138—150° (0·5 g.). Materials (A) and (B) were washed with acetone, giving the *α-ester* (1·00 g.), m. p. 152—154°, which crystallised from benzene–light petroleum (b. p. 60—80°) in needles (Found: C, 54·85; H, 5·2; Cl, 10·9; *C*-Me, 5·35. $C_{15}H_{17}O_6Cl$ requires C, 54·8; H, 5·2; Cl, 10·8; 1*C*-Me, 4·6%).

The gum obtained from the mother-liquors was fractionally crystallised from ether, giving impure material (0·8 g.) and the *β-ester* (0·90 g.) as needles, m. p. 83—86° (Found: C, 54·5; H, 5·4; Cl, 10·9; *C*-Me, 5·6%). The m. p. was not depressed on admixture with optically active methyl 7-chloro-4 : 6-dimethoxy-3-oxocoumaran-2-β-butyrate (see below) prepared from griseofulvin; in chloroform the infrared spectra were identical, and distinct from the spectrum of the α-ester.

Interconversion of the esters. The β-ester (100 mg.), anhydrous potassium carbonate (0·5 g.), and acetone (10 ml.) were heated together under reflux for 7 hr. Recovery and fractional crystallisation from benzene–light petroleum (b. p. 60—80°) gave the α-ester (36 mg.), m. p. 138—147°, raised to 150—152° by further crystallisation. Crystallisation of the more soluble fractions from ether gave the β-ester (41 mg.), m. p. 83—85°.

Similar results were obtained with the α-ester. The esters were not interconverted by seeded crystallisation or in toluene under reflux for 5 hr.

7-Chloro-4 : 6-dimethoxy-3-oxocoumaran-2-β-butyric Acid (V; R = Cl, R′ = R″ = H).—(i) The above α-ester (561 mg.) was boiled with N-hydrochloric acid (25 ml.) for 3 hr., water (20 ml.) being added after 2·5 hr. The filtered, water-washed product (495 mg.), m. p. 154—162° (decomp.), was used for further work. A specimen was crystallised from toluene, precipitated from solution in sodium hydrogen carbonate by acidification with hydrochloric acid, and recrystallised, giving the *acid* as needles, m. p. 151—154° (decomp.), the decomp. point depending on the rate of heating and not being depressed on admixture with the optically active acid from griseofulvin [11] (Found: C, 53·2; H, 5·05; Cl, 11·3; OMe, 20·4%; equiv., 305. $C_{14}H_{15}O_6Cl$ requires C, 53·45; H, 4·75; Cl, 11·3; 2OMe, 19·7%; *M*, 315).

(ii) Hydrolysis of the β-ester (500 mg.) in the same way gave the same acid (460 mg.), m. p. and mixed m. p. 150—157° (Found: C, 53·5; H, 5·0; Cl, 11·4; OMe, 19·1%). The infrared spectra of the acids from (i) and (ii) were identical.

The acid (100 mg.) from (i) with diazomethane gave a mixture separated into the α-ester (47 mg.; m. p. 142—150°) and the β-ester (38 mg.; m. p. 82—85°) by crystallisation.

Methylation of the acid from (ii) gave similar results.

7-Chloro-6-hydroxy-4-methoxy-3-oxocoumaran-2-β-butyric Acid (VII).—7-Chloro-4 : 6-dimethoxy-3-oxocoumaran-2-β-butyric acid (234 mg.) was boiled with N-sodium hydroxide (10 ml.) for 4 hr. After cooling, filtration, and acidification of the filtrate, the precipitated solid (123 mg.) was collected and crystallised from ethyl acetate in prisms of the phenolic acid, m. p. 212—214° (decomp.), not depressed on admixture with material prepared from griseofulvin [11] (Found: C, 51·9; H, 4·4; Cl, 11·1; OMe, 10·3. $C_{13}H_{13}O_6Cl$ requires C, 51·9; H, 4·3; Cl, 11·8; OMe, 10·3%), $\nu_{max.}$ (dilute chloroform solution) 1701 (C=O), 1737 cm.$^{-1}$ (shoulder, monomeric CO_2H).

7-Chloro-2-hydroxy-4 : 6-dimethoxy-3-oxocoumaran-2-β-butyric Acid (V; R = Cl, R′ = OH, R″ = H).—A solution of 7-chloro-4 : 6-dimethoxy-3-oxocoumaran-2-β-butyric acid (134 mg.) in N-sodium carbonate (10 ml.) was treated with 4·5% aqueous potassium permanganate (3·0 ml.) at 1—2° during 1·5 hr. The mixture was kept at 0° for 1·5 hr., excess of permanganate decomposed with sulphur dioxide, and the filtered solution acidified with hydrochloric acid. The gummy product, recovered in ether, was treated with a little ether, and the resultant solid [85 mg.; m. p. 179—182° (decomp.)] crystallised from ethyl methyl ketone–light petroleum (b. p. 60—80°) in needles of the *hydroxy-acid*, m. p. 189—190° (decomp.) (Found: C, 51·1; H, 4·6; Cl, 10·65. $C_{14}H_{15}O_7Cl$ requires C, 50·8; H, 4·6; Cl, 10·7%). The m. p. was not depressed on admixture with a specimen of the acid obtained from griseofulvin as described previously [11,12] and the infrared spectra of the two products were identical.

Dehydration.—The above hydroxy-acid (85 mg.) was kept with acetic anhydride (0·3 ml.) and pyridine (0·7 ml.) at 35° for 3 days. The product obtained by dilution with water at 0° was washed with sodium hydrogen carbonate solution and with water, giving the *lactone* (VIII; R = Cl) (61 mg.). It crystallised from ethyl acetate as needles, m. p. 223—224°, not depressed on admixture with lactone (A) obtained from griseofulvin [11] (Found: C, 53·6; H, 4·2; Cl, 11·4. $C_{14}H_{13}O_6Cl$ requires C, 53·7; H, 4·2; Cl, 11·3%). The infrared spectrum was indistinguishable from that of lactone (A). The lactone was also obtained by sublimation of the hydroxy-acid at 190—210°/10^{-4} mm.

Methyl 4 : 6-Dimethoxy-3-oxocoumaran-2-β-butyrate (V; R = R′ = H, R″ = Me).—N-Methanolic sodium methoxide (2·0 ml.) was added to 4 : 6-dimethoxycoumaranone (1·94 g.) and methyl crotonate (1·00 g.) in dioxan (40 ml.) at 24°. After 24 hr. the mixture was acidified with acetic acid and evaporated *in vacuo*. An ethereal solution of the residue was washed with sodium hydrogen carbonate solution and with water, and the oily product recovered by evaporation was chromatographed on alumina (22 × 1·5 cm.) in ether. A band fluorescing blue was eluted with ether–methanol (100 : 1), giving, on recovery, a syrup (1·7 g.). The syrupy ester (2·3 g.) from several experiments was kept with ether, giving a solid (1·0 g.) which crystallised from benzene–ether in prisms, m. p. 88—89°, of the *α-ester* (Found: C, 61·2; H, 6·2; OMe, 30·8. $C_{15}H_{18}O_6$ requires C, 61·2; H, 6·2; 3OMe, 31·6%).

The syrup recovered from the ethereal mother-liquor did not crystallise and distilled as a very pale yellow syrup (180—210°/10^{-3} mm.) (Found: C, 61·1; H, 6·2%). It is considered to consist essentially of the β-ester.

Ethyl 4 : 6-Dimethoxy-3-oxocoumaran-2-β-butyrate (V; R = R′ = H, R″ = Et).—2N-Ethanolic sodium ethoxide (0·43 ml.) was added to 4 : 6-dimethoxycoumaran-3-one (1·00 g.) and ethyl crotonate (0·59 g.) in dioxan (18 ml.) at 20°. After 48 hr. a little tar was filtered off;

the filtrate was acidified with acetic acid, and the product recovered and chromatographed (elution of a purple-fluorescing band) as described above for the methyl ester. The *ester* was obtained as an oil (1·00 g.) which was distilled at 190°/10^{-3} mm. (Found: C, 62·1; H, 6·6; *C*-Me, 8·1. $C_{16}H_{20}O_6$ requires C, 62·3; H, 6·5; 2*C*-Me, 9·8%).

4 : 6-*Dimethoxy*-3-*oxocoumaran*-2-β-*butyric Acid* (V; R = R′ = R″ = H).—The above ester (1·50 g.) was boiled with 3N-hydrochloric acid (20 ml.) for 5 hr. The cooled mixture was made alkaline, washed with ether, and acidified. The crude orange gummy product (1·19 g.) recovered in ether was distilled (200°/10^{-3} mm.), giving a pale yellow hygroscopic glass which consisted essentially of the required acid but contained a phenolic impurity (ferric reaction) (Found: C, 60·3; H, 5·7; OMe, 18·2. Calc. for $C_{14}H_{16}O_6$: C, 60·0; H, 5·75; 2OMe, 22·1%).

Hydrolysis with weaker hydrochloric acid lessened but did not eliminate the formation of the impurity.

The ethyl ester (Found: C, 62·5; H, 6·8. Calc. for $C_{16}H_{20}O_6$: C, 62·3; H, 6·5%) was identical (infrared spectrum) with material prepared as described above.

2-*Hydroxy*-4 : 6-*dimethoxy*-3-*oxocoumaran*-2-β-*butyric Acid* (V; R = R″ = H, R′ = OH).—The above acid (350 mg.) in N-sodium carbonate (22 ml.) was treated with 4·5% potassium permanganate solution (7·6 ml.) at 1—2° during 2 hr. After 4 hr. at 0° the product was recovered as described for the chlorine-containing analogue, giving a solid (193 mg.) which crystallised from ethyl acetate–light petroleum (b. p. 60—80°) in needles (70 mg.) of the *hydroxy-acid*, m. p. 169—173° (decomp.) (Found: C, 56·9; H, 5·7; OMe, 21·4%; equiv., 276. $C_{14}H_{16}O_7$ requires C, 56·75; H, 5·4; 2OMe, 20·9%; *M*, 296). The acid gave no colour with ferric chloride.

Dehydration of the hydroxy-acid (112 mg.) as described for the chlorine-containing analogue gave the *lactone* (VIII; R = H) (85 mg.), prisms (from ethyl acetate–light petroleum), m. p. 150—151° (Found: C, 60·3; H, 5·4; OMe, 22·6. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·1; 2OMe, 22·3%). The m. p. was not depressed by mixture with the lactone obtained from dechlorogriseofulvin,[3] and the infrared spectra of the two products were indistinguishable.

Alkaline Oxidation of Ethyl **4 : 6-*Dimethoxy*-3-*oxocoumaran*-2-β-*butyrate***.—An ice-cold stirred suspension of the ester (525 mg.) in N-sodium carbonate (30 ml.) was treated dropwise with 5% potassium permanganate solution, but only a few drops were decolorised. After the addition of dioxan (25 ml.) addition of the permanganate was continued (10·0 ml., in 1 hr.). The mixture was kept overnight at 0°, then decolorised with sulphur dioxide and filtered. The filtrate and acetone washings of the cake were evaporated *in vacuo*, sodium hydroxide solution was added, and starting material (0·2 g.) was recovered in ether. The aqueous fraction was acidified; the product recovered by ether-extraction crystallised from ether, giving the lactone (VIII; R = H) (45 mg.), m. p. 141—142°, raised to 150—151° (34 mg.) by crystallisation from ethyl methyl ketone. The lactone was identical (mixed m. p. and infrared spectrum) with material obtained as described above.

Attempted Ring Closure of Ethyl **4 : 6-*Dimethoxy*-2-(1-*methyl*-3-*oxobutyl*)-3-*oxocoumaran*-2-*carboxylate*** (IX; R = R′ = OMe).—Attempted ring closure with sodium ethoxide in the absence or presence of ethanol, sodium, triphenylmethylsodium, sodamide, potassium *tert.*-butoxide, concentrated sulphuric acid, or polyphosphoric acid failed. Similar results were obtained with the analogue (IX; R = R′ = H).

(−)7-*Chloro*-4 : 6-*dimethoxy*-3-*oxocoumaran*-2-β-*butyric Acid*.—The optically active acid obtained from griseofulvin [11] gave the *methyl ester* as prisms, m. p. 96—98° (from ether), $[\alpha]_D^{22}$ −19° ± 3° (*c* 0·84 in acetone) (Found: C, 55·0; H, 5·4; Cl, 10·8. $C_{15}H_{17}O_6Cl$ requires C, 54·8; H, 5·2; Cl, 10·8%).

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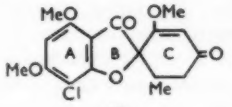
440. *Griseofulvin. Part XVII.*[1] *Synthesis of 7-Chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione.*

By A. W. Dawkins and T. P. C. Mulholland.

The synthesis is described of grisan and coumaran-3-one *spirocyclo*pentane analogues of some griseofulvin derivatives, and of racemates of the griseofulvin degradation products, (*l*,*d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3-one * (II) and (*d*,*d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione (III).

The preceding paper[1] described a synthesis of the racemate of (*l*,*d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3-one * (II), the racemate of a product obtained from (*l*,*d*)-griseofulvin (I). In the present paper details are given of a second route[3] which led to the synthesis of the racemates of the (*l*,*d*)-ketone (II) and of (*d*,*d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione (III). This route was based on reports[4,5] that the usnolic acid analogue (IV; R = R′ = Me) obtained by ring closure of the keto-ester (V; R = R′ = Me) with sulphuric acid[4,5,6] was a spiran rather than a dihydrodibenzofuran derivative. Ozonolysis of the ester (IV; R = R′ = Me) gave formaldehyde and a compound shown to be a coumaranone ester[5] (VI; R = R′ = Me, R″ = CO_2Et) by spectroscopy and oxidation to a salicylic acid. Since grisans containing a *C*-methyl group in the correct position for derivatives of griseofulvin might be obtained by this route, it was further investigated.



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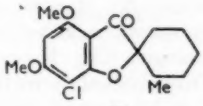

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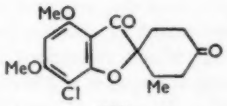

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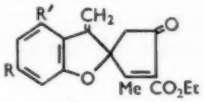

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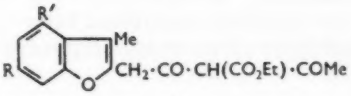

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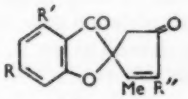


(VI)

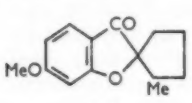
(i) The synthesis[6] of the ester (IV; R = OMe, R′ = H) was extended to give the spiran (VII). The orientation of the formyl group in the intermediate aldehyde (VIII; R = R′ = H, R″ = CHO), previously[6] based on a mixed decomposition point of the corresponding acid (VIII; R = R′ = H, R″ = CO_2H), was confirmed by comparison of its ethyl ester with an authentic specimen of ethyl 6-methoxy-3-methylcoumaranone-2-carboxylate. The keto-ester (V; R = OMe, R′ = H) obtained[6] from the above aldehyde was cyclised with sulphuric acid to the spiran (IV; R = OMe, R′ = H) either directly[6] or through its copper chelate. The spiran showed strong absorption at 328 mμ (log ε 3·98), assumed to be due to the exocyclic methylene group conjugated with the aromatic ring. In this it resembled the analogue (IV; R = R′ = Me). The dihydro-derivative (IX) showed only weak absorption (C=C–C=O, R band) at 321 mμ. Ozonolysis of the ester (IV; R = OMe, R′ = H) gave formaldehyde and the coumaranone ester (VI; R = OMe, R′ = H, R″ = CO_2Et), which no longer showed absorption at 1649 $cm.^{-1}$ (=CH_2) but

* Concerning (*l*,*d*) see footnote, p. 2203, and ref. 2.

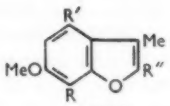
[1] Part XVI, Dawkins and Mulholland, preceding paper.
[2] MacMillan, *J.*, 1959, 1823.
[3] Dawkins and Mulholland, XVIth Internat. Congr. Pure Appl. Chem., Paris, 1957.
[4] Dean, *Sci. Prog.*, 1952, **40**, 653.
[5] Dean, Halewood, Mongkolsuk, Robertson, and Whalley, *J.*, 1953, 1250.
[6] Foster, Robertson, and Healy, *J.*, 1939, 1594.

possessed an additional band at 1715 cm.$^{-1}$ ascribed to the chemically unreactive carbonyl group of a coumaran-3-one. The ultraviolet spectrum was almost identical with that of 6-methoxycoumaran-3-one. Oxidation of this ester (VI; R = OMe, R′ = H, R″ = CO_2Et) gave 2-hydroxy-4-methoxybenzoic acid, and acidic hydrolysis gave the acid (VI; R = OMe, R′ = H, R″ = CO_2H) which was decarboxylated to the unsaturated ketone (VI; R = OMe, R′ = R″ = H). Hydrogenation of the latter with a palladium–carbon catalyst gave a low yield of the *cyclo*pentane (VII). This was identical with the racemate of 6-methoxy-3-oxocoumaran-2-*spiro*-1′-(2′-methyl*cyclo*pentane) obtained previously [1] by condensation of 6-methoxycoumaranone with 1 : 4-dibromopentane.

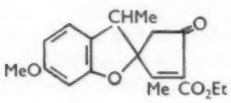
(ii) *Grisans.* For the synthesis of grisans the required 2-propionic acid (VIII; R = R′ = H, R″ = $[CH_2]_2{\cdot}CO_2H$) was obtained directly from 6-methoxy-3-methylcoumarone [6] with β-propiolactone. The entering group was shown to occupy the 2-position by chain-lengthening of the known 6-methoxy-3-methylcoumarone-2-acetic acid (VIII; R = R′ = H, R″ = $CH_2{\cdot}CO_2H$).



(VII)

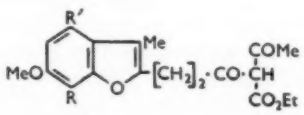


(VIII)

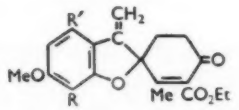


(IX)

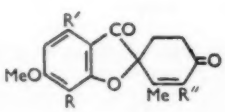
Condensation of the acid chloride of the 2-propionic acid with ethyl ethoxymagnesioacetoacetate (cf. ref. 5) gave a mixture of the ester (VIII; R = R′ = H, R″ = $[CH_2]_2{\cdot}CO_2Et$) and the required keto-ester (X; R = R′ = H). The latter was cyclised by sulphuric acid [6] or, better, polyphosphoric acid to the methylenespiran ester (XI; R = R′ = H) which resembled its analogue (IV; R = OMe, R′ = H) chemically and showed strong absorption at 326 mμ. Ozonolysis of the methylene ester gave the coumaranone (XII; R = R′ = H, R″ = CO_2Et) which showed ultraviolet absorption very similar to that of 6-methoxycoumaranone. Acidic hydrolysis of the ester with simultaneous decarboxylation gave the non-crystalline unsaturated ketone (XII; R = R′ = R″ = H) characterised as the 2 : 4-dinitrophenylhydrazone. Hydrogenation of this ketone gave an intractable product.



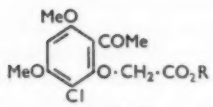
(X)



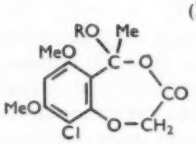
(XI)



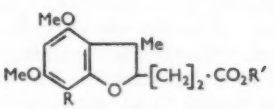
(XII)



(XIII)



(XIV)

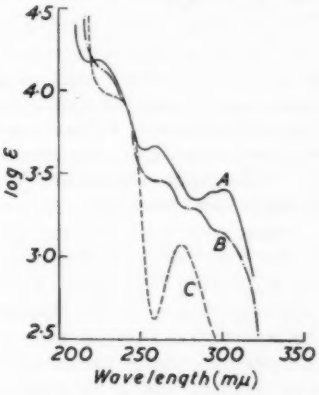


(XV)

For grisans more closely related to griseofulvin, 3-chloro-2-hydroxy-4 : 6-dimethoxyacetophenone [7] was used as starting material. Condensation with the appropriate chloro- or bromo-ester gave the phenoxyacetates (XIII; R = Et, and R = Me). Acidic hydrolysis of the phenoxyacetates gave one of two isomeric acids $C_{12}H_{13}O_6Cl$ (XIII and XIV; R = H) both with m. p. 144°, or an inseparable mixture of the two (m. p. 119—120°). Ethanolic sulphuric acid gave the open form (XIII; R = H); with 3N-hydrochloric acid the product consisted of the cyclic form (XIV; R = H). Hydrolysis with N-hydrochloric

acid gave a substance shown to be a 1 : 1 mixture of the two acids by analysis and spectroscopy. The ultraviolet spectra of the two forms of the acid were distinct (see Figure), the acetophenone chromophore of diminished intensity shown by acid (XIII; R = H) being absent from the spectrum of the cyclic form. Although the infrared spectra of the cyclic acid and its esters showed only a single C=O band [*e.g.*, (XIV; R = Me), 1742 cm.$^{-1}$], the open form [*e.g.*, (XIII; R = Et)] showed, besides absorption at 1648 cm.$^{-1}$ (acetophenone C=O), a doublet both as a solid (1763, 1753 cm.$^{-1}$) and, at a higher frequency, in solution. Investigation of model compounds [8] showed that the doublet occurred generally in substituted phenoxy- and alkoxy-acids and their esters.

Dehydration of both forms of the acid gave the coumarone (VIII; R = Cl, R′ = OMe, R″ = H) which condensed with β-propiolactone to give the required 2-propionic acid (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2 \cdot CO_2H$), but the yield was low and could not be improved. Attempts to orientate the entering group by two Arndt–Eistert syntheses from the carboxylic acid (VIII; R = Cl, R′ = OMe, R″ = CO_2H) failed, but a better synthesis of the 2-propionic acid which served for orientation was as follows. Reaction of the coumarone with hydrogen cyanide gave the 2-formyl derivative (VIII; R = Cl, R′ = OMe, R″ = CHO) whose structure was proved by oxidation and esterification to



Ultraviolet absorption spectra of (A) compound (XIII; R = H), *(C) compound* (XIV; R = H), *and (B) a* 1 : 1 *mixture thereof.*

ethyl 7-chloro-4 : 6-dimethoxy-3-methylcoumarone-2-carboxylate (VIII; R = Cl, R′ = OMe, R″ = CO_2Et) identical with authentic material obtained by ring closure of the ester (XIII; R = Et). The aldehyde was converted into the 2-acrylic acid (VIII; R = Cl, R′ = OMe, R″ = $CH{:}CH \cdot CO_2H$) which was selectively reduced to the 2-propionic acid (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2 \cdot CO_2H$) identical with material prepared by the first method.

Selective hydrogenation of the 2-acrylic acid was first accomplished in the presence of a nickel catalyst,[9] but the insolubility of the acid in organic solvents made this method impracticable on a larger scale. Hydrogenation of the sodium salt of the acid in aqueous solution with a palladium–strontium carbonate catalyst [10] gave satisfactory results in early experiments, but later, from the purified acid, it gave a complex mixture from which, besides the desired product, its dechloro-analogue (VIII; R = H, R′ = OMe, R″ = $[CH_2]_2 \cdot CO_2H$) and the coumarans (XV; R = Cl, R′ = H; and R = R′ = H) were also isolated. Both the coumaran acid (XV; R = R′ = H) and the corresponding ester (XV; R = H, R′ = Me) were dehydrogenated to the corresponding coumarones with sulphur and chloranil respectively. The required selective reduction was shown to occur if a little piperidine was added to the pure acid. Presumably piperidine was present in

[8] Dawkins and Duncanson, unpublished work.
[9] Burdick and Adkins, *J. Amer. Chem. Soc.*, 1934, **56**, 438.
[10] Martin and Robinson, *J.*, 1943, 491.

the acid obtained from the Doebner condensation, but the addition of piperidine to the pure acid did not give yields as high as those which had been obtained from the impure acid.

The 2-propionyl chloride (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2$·COCl) condensed with ethyl ethoxymagnesioacetoacetate, giving the keto-ester (X; R = Cl, R′ = OMe). Since direct cyclisation of the keto-ester with sulphuric or polyphosphoric acid failed, it was treated with cupric acetate, giving a mixture of the isomeric α- (80—90%) and β-copper chelates. The β-chelate (m. p. 98—100°) was converted into the α-chelate (m. p. 164°) when heated at 120—130°. The ester carbonyl band (1739 cm.$^{-1}$ in the keto-ester) was absent from the infrared spectra of both chelates, suggesting that this group acted in a donor capacity in both cases together with one of the carbonyl groups. A band at 1623 cm.$^{-1}$, present in both the chelates and the keto-ester, is evidently due to bonded carbonyl as in acetylacetone.[11] Cyclising the β-chelate with polyphosphoric acid at room temperature, or the α-chelate at 70—80°, gave the methylenespiran ester (XI; R = Cl, R′ = OMe) in *ca.* 40% yield. When the α-chelate was treated with polyphosphoric acid at room temperature none of the required ester was obtained, the product containing starting material (30%), (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2$·CO_2H) (30%), the corresponding ethyl ester (10%) and traces of the ketone (VIII; R = Cl, R′ = OMe, R″ = CH_2·COMe).

The properties of the methylenespiran ester were consistent with the structure assigned to it. As with other members of the chlorine-containing series, the ultraviolet spectra showed a bathochromic shift compared with the 6-methoxy-analogues. Ozonolysis and reduction of the ozonide with zinc–acetic acid gave a mixture of starting material (5%), 3-chloro-2-hydroxy-4 : 6-dimethoxyacetophenone (40%), a chlorine-free acidic fraction (30%) and, surprisingly, the crystalline coumaranone (XII; R = Cl, R′ = OMe, R″ = H) (4%). The infrared spectrum [1718 cm.$^{-1}$ (coumaranone CO) and 1684 cm.$^{-1}$ (C=C–CO)] and ultraviolet spectrum were consistent with this structure. Hydrolysis of the ozonide with water gave the coumaranone ester (XII; R = Cl, R′ = OMe, R″ = CO_2Et) which, however, could not be hydrolysed to the free acid. The ready hydrolytic decarboxylation occurring during hydrolysis of the ozonide with zinc–acetic acid is unexplained.

Hydrogenation of the coumaranone (XII; R = Cl, R′ = OMe, R″ = H) with a palladium–carbon catalyst gave an alcohol fraction (which was not investigated owing to the stereochemical complications due to the presence of three asymmetric centres), a monoketone, and a diketone. The monoketone was identical with the synthetic racemate[1] of (*l*,*d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3-one (II). On the other hand the infrared spectrum of the diketone in solution was distinct from that of (*l*,*d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione[12] (III) but was identical with that of the (*d*,*d*)-diketone[13] (III). The synthetic diketone is therefore the racemate of the latter. It is presumed that the formation of only one racemate of (II) and (III), but of different configuration, must be due to simultaneous competing reduction mechanisms.

Experimental

M. p.s are corrected. Microanalyses are by Messrs. W. Brown and A. G. Olney. Absorption spectra (in ethanol) and alumina for chromatography were obtained as described previously.[1] Unless otherwise stated, infrared spectra were determined for Nujol " mulls "; chromatography was carried out in ultraviolet light; light petroleum had b. p. 40—60°.

Ethyl 6-hydroxy-3-methylcoumarone-2-carboxylate, prepared (60% yield) by Hantszch's method,[14] formed prisms, m. p. 179°, from ethanol (lit., m. p. 178°) (Found: C, 65·4; H, 5·6. Calc. for $C_{12}H_{12}O_4$: C, 65·4; H, 5·5%), $\nu_{max.}$ 1700 cm.$^{-1}$, $\lambda_{max.}$ 313, 282, 241, 210 mμ (log ε 4·30, 4·07, 3·90, 4·24).

[11] Gordy, *J. Chem. Phys.*, 1940, **8**, 516.
[12] Dawkins and Mulholland, *J.*, 1959, 1830.
[13] Mulholland, *J.*, 1952, 3994.
[14] Hantszch, *Ber.*, 1886, **19**, 292.

Treatment with dimethyl sulphate gave the methoxy-acid (VIII; R = R′ = H, R″ = CO_2H) (30%) and the corresponding ethyl ester (25%). The latter formed needles, m. p. 74—75°, from ethanol (lit.,[14] m. p. 74°) (Found: C, 66·5; H, 6·1. Calc. for $C_{13}H_{14}O_4$: C, 66·65; H, 6·0%), $\nu_{max.}$ 1700 cm.$^{-1}$, $\lambda_{max.}$ 312, 285, 243 mμ (log ε 4·44, 4·13, 3·97). The methoxy-acid, m. p. 184°, was identical (infrared spectrum) with the oxidation product of 2-formyl-6-methoxy-3-methylcoumarone, and esterification gave the above ethyl ester, m. p. 74°.

Ethyl α-acetyl-β-oxo-6-methoxy-3-methylcoumarone-2-γ-butyrate[6] (V; R = OMe, R′ = H) prepared from 6-methoxy-3-methylcoumarone-2-acetyl chloride and ethyl ethoxymagnesioacetoacetate,[5] was an orange-red oil, $\nu_{max.}$ 1714, 1623, and 1587 cm.$^{-1}$. The *copper derivative*, obtained by shaking an ethereal solution of the keto-ester with aqueous cupric acetate, formed greenish-blue plates, m. p. 175°, from methanol (Found: C, 68·4; H, 5·8. $C_{36}H_{38}O_8Cu$ requires C, 68·6; H, 6·1), $\nu_{max.}$ 1715, 1692, 1671, and 1587 cm.$^{-1}$.

Ethyl 6-Methoxy-3-methylenecoumaran-2-spiro-1′-(2′-methyl-4′-oxocyclopent-2′-en-3′-carboxylate) (IV; R = OMe, R′ = H).—A mixture of the above keto-ester (7 g.) and concentrated sulphuric acid (15 ml.) was kept at −5° for 3 days, then diluted with water (50 ml.) and extracted with ether. Extraction of the ethereal solution with sodium hydrogen carbonate solution and acidification of the alkaline extract gave 6-methoxy-3-methylcoumarone-2-acetic acid (200 mg.), m. p. 139—140°, identified by mixed m. p., analysis, and spectra. Recovery from the ether extract gave a pale yellow oil, which after passage through a charcoal column in ethanol, was obtained crystalline by prolonged trituration under light petroleum (b. p. 80—100°) at −50°. Further recrystallisation at room temperature gave the methylene ester as needles (2·8 g.), m. p. 122° (lit.,[5] m. p. 122°) (Found: C, 68·7; H, 6·0; OMe, 19·1. Calc. for $C_{18}H_{18}O_5$: C, 68·8; H, 5·8; OAlk as OMe, 19·5%), $\nu_{max.}$ 1745, 1707, 1649, 1615, 1595 cm.$^{-1}$, $\lambda_{max.}$ 327, 263, 231, 214 mμ (log ε 3·98, 4·12, 4·35, 4·31). The ester gave an intense positive Ehrlich reaction, and decolorised permanganate. The 2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 175—176°, from benzene–light petroleum (b. p. 60—80°) (Found: N, 11·1. $C_{24}H_{22}O_8N_4$ requires N, 11·3%). The methylene ester was obtained in slightly higher yield (*ca.* 45%) by cyclisation of the copper derivative with sulphuric acid. Attempts to hydrolyse the ester with alcoholic hydrochloric acid failed.

Hydrogenation of the Ester (IV; R = OMe, R′ = H).—One mol. of hydrogen was absorbed when the ester (150 mg.) was hydrogenated at room temperature and pressure with a catalyst prepared *in situ* from palladium chloride (7 mg.) and charcoal (75 mg.) in acetic acid (10 ml.). The recovered gum was chromatographed in ether on alumina (pH 7; 10 × 0·5 cm.). Elution with ether and repeated trituration of the product under light petroleum at 0° gave plates (105 mg.) of *ethyl 6-methoxy-2-methylcoumaran-2-spiro-1′-(2′-methyl-4′-oxocyclopent-2′-en-3′-carboxylate)* (IX), m. p. 77—78° after recrystallisation from the same solvent (Found: C, 68·6; H, 6·35. $C_{18}H_{20}O_5$ requires C, 68·3; H, 6·4%), $\nu_{max.}$ 1738, 1698, 1610 cm.$^{-1}$, $\lambda_{max.}$ 320, 302, 281, ~263, 228 mμ (log ε 2·78, 3·45, 3·59, 3·72, 4·25). The compound did not give a blue colour with Ehrlich's reagent and was unsaturated to neutral permanganate. The 2 : 4-*dinitrophenylhydrazone* formed orange plates, m. p. 160°, from benzene–light petroleum (Found: N, 11·1. $C_{24}H_{24}O_8N_4$ requires N, 11·3%).

Ethyl 6-Methoxy-3-oxocoumaran-2-spiro-1′-(2′-methyl-4′-oxocyclopent-2′-en-3′-carboxylate) (VI; (R = OMe, R′ = H, R″ = CO_2Et).—A stream of ozone–oxygen was passed into a solution of the preceding ester (500 mg.) in carbon tetrachloride (30 ml.) until the solution became opaque. Evaporation of the filtered solution *in vacuo* gave a gum which was mixed with cold water (25 ml.) and kept for 24 hr. Distillation of the aqueous fraction into a saturated solution of dimedone in 10% aqueous ethanol gave the derivative of formaldehyde as needles, m. p. and mixed m. p. 191—192°: (infrared spectrum). An ethereal solution of the residual gum was chromatographed on alumina (pH 7; 15 × 1 cm.). The lowest bright-blue fluorescent band was eluted with ether and recovered, the product giving rosettes (110 mg.) when boiled with light petroleum. The following band fluorescing greenish-blue gave slightly impure material (100 mg.). Recrystallisation of the combined product from light petroleum (b. p. 60—80°) gave the *ester* (VI; R = OMe, R′ = H, R″ = CO_2Et) (200 mg.), m. p. 115—117° (Found: C, 64·5; H, 5·3. $C_{17}H_{16}O_6$ requires C, 64·55; H, 5·1%), $\nu_{max.}$ 1751, 1715, and 1701 cm.$^{-1}$, $\lambda_{max.}$ 321, 275, 232 mμ (log ε 3·98, 4·21, 4·23). The compound gave an orange-red nitroprusside and a negative Ehrlich reaction: it reduced Fehling's solution and gave no blue colour with concentrated nitric acid. The *mono*-2 : 4-*dinitrophenylhydrazone* formed yellow plates, m. p. 243° (decomp.), from benzene–light petroleum (b. p. 60—80°) (Found: N, 11·1. $C_{23}H_{20}O_9N_4$

requires N, 11·3%). Oxidation of the ester (100 mg.) with Fehling's solution (cf. ref. 5) gave 2-hydroxy-4-methoxybenzoic acid (25 mg.), m. p. 154—155° (lit.,[15] m. p. 152—154°).

6-*Methoxy*-3-*oxocoumaran*-2-spiro-1′-(2′-*methyl*-4′-*oxo*cyclo*pent*-2′-*ene*-3′-*carboxylic Acid*) (VI; R = OMe, R′ = H, R″ = CO_2H).—The ester (VI; R = OMe, R′ = H, R″ = CO_2Et) (70 mg.) was heated under reflux for 6 hr. with 2N-hydrochloric acid (17·5 ml.) and ethanol (14 ml.) under nitrogen. On cooling, the pale yellow product separated (15 mg.). Removal of ethanol *in vacuo* gave more product (15 mg.) together with starting material (30 mg.). Purification of the product by way of the sodium salt and recrystallisation from ethanol gave colourless needles (23 mg.) of the *acid*, m. p. 175—177° (Found: C, 62·5; H, 4·0%; equiv., 284. $C_{15}H_{12}O_6$ requires C, 62·5; H, 4·2%; *M*, 288), $\nu_{max.}$ 1716, and 1697 cm.$^{-1}$, $\lambda_{max.}$ 318, 273, 232, 210 mμ (log ε; 4·05, 4·25, 4·30, 4·45).

6-*Methoxy*-3-*oxocoumaran*-2-spiro-1′-(2′-*methyl*cyclo*pent*-2′-*en*-4′-*one*) (VI; R = OMe, R′ = R″ = H).—The above acid (70 mg.) was heated in a modified sublimation tube at 190—200° in a stream of nitrogen for 10 min. Sublimation of the residue *in situ* at 190°/10^{-4} mm. gave the cyclo*pentenone* (VI; R = OMe, R′ = R″ = H), which formed pale yellow needles (40 mg.), m. p. 193—195° from aqueous acetone (Found: C, 68·9; H, 5·2. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·95%), $\nu_{max.}$ 1713 cm.$^{-1}$, $\lambda_{max.}$ 320, 273, 232, 209 mμ (log ε 3·92, 4·07, 4·16, 4·40). The 2 : 4-*dinitrophenylhydrazone* formed orange-red plates, m. p. 238—240°, from ethyl acetate (Found: N, 13·1. $C_{20}H_{16}O_7N_4$ requires N, 13·2%). Decarboxylation was also carried out in *p*-cymene at the b. p. for 1 hr.

Reduction of the cyclo*Pentenone* (VI; R = OMe, R′ = R″ = H).—The ketone (15 mg.) in ethyl acetate (1·5 ml.) was added to a previously reduced catalyst prepared from palladium chloride (10 mg.) and charcoal (40 mg.) in water (1 ml.), and the mixture was shaken at room temperature and pressure in an atmosphere of hydrogen until absorption ceased (2·4 mol. in 5 min.). Recovery gave a pale yellow gum (13 mg.) which was chromatographed in benzene on alumina (pH 4; 4 × 0·5 cm.).

A bright blue-fluorescent band was eluted with benzene and gave a colourless glass (2 mg.) on recovery. Sublimation followed by crystallisation from light petroleum gave prisms (0·8 mg.), m. p. 167—168°, of 6-*methoxy*-3-*oxocoumaran*-2-spiro-1′-(2′-*methyl*cyclo*pentane*) (VII), identical (mixed m. p. and infrared spectrum) with the product from condensation of 6-methoxycoumaran-3-one and 1 : 4-dibromopentane.[1]

6-*Methoxy*-3-*methylcoumarone*-2-β-*propionic Acid* (VIII; R = R′ = H, R″ = $[CH_2]_2{\cdot}CO_2H$).—(i) A mixture of β-propiolactone (7·5 ml., 8·64 g.) and 6-methoxy-3-methylcoumarone (19·44 g.) was heated under reflux for 6 hr. at 200°. The cooled residue was ground with sodium carbonate solution. The mixture was filtered, the ether-washed filtrate was acidified, and the precipitated product (5·3 g.) collected. Sublimation at 130°/10^{-4} mm. and crystallisation from dilute ethanol gave the *acid* (4·9 g.) as colourless plates, m. p. 137° (Found: C, 66·5; H, 6·2%; equiv., 231. $C_{13}H_{14}O_4$ requires C, 66·65; H, 6·0%; *M*, 234), $\nu_{max.}$ 1707 cm.$^{-1}$, $\lambda_{max.}$ 292, 253 mμ (log ε 3·80, 4·16). The acid gradually gave a red-violet colour in concentrated sulphuric acid. Starting material (10 g.) was recovered from the carbonate-insoluble fraction.

(ii) 6-Methoxy-3-methylcoumarone-2-acetic acid (440 mg.) and redistilled thionyl chloride (1 ml.) were warmed gently together until a clear solution was obtained. Volatile products were removed *in vacuo* below 30° and the residual red oil in ether (10 ml.) was added at 0° to a 3-fold excess of diazomethane in ether (15 ml.) and kept at 0° for 24 hr. Removal of the ether *in vacuo* gave pale yellow needles of the diazo-ketone, m. p. 118—123°.

The crude product in dioxan (10 ml.) was added dropwise to a mechanically stirred suspension of freshly prepared silver oxide (2 g.) in a solution of sodium thiosulphate (1 g.) and potassium carbonate (1 g.) in water (20 ml.) at 50—60°. Nitrogen was evolved and after 20 min. the temperature was raised to 70° for 10 min., then to 90° for 5 min. After filtration, acidification with dilute nitric acid caused separation of a brown oil, which partly solidified on trituration with water. Sublimation of the semisolid material at 100—130°/10^{-4} mm., followed by crystallisation of the sublimate from dilute ethanol, gave the acid (60 mg.), m. p. 137—138°, identical (mixed m. p. and infrared spectrum) with material obtained by method (i) (Found: C, 66·5; H, 6·3%).

Ethyl 6-*Methoxy*-2′-*methyl*-3-*methylene*-4′-*oxogris*-2′-*en*-3′-*carboxylate* (XI; R = R′ = H).—The above acid was converted into the green oily acid chloride with phosphorus pentachloride

[15] Kostanecki and Tambor, *Ber.*, 1895, **28**, 2307.

XUM

by the method described above. The *amide* formed plates from benzene–light petroleum (b. p. 60—80°) (Found: N, 6·1. $C_{13}H_{15}O_3N$ requires N, 6·0%).

A solution of the acid chloride in ether (500 ml.) was mixed with a suspension of ethyl ethoxymagnesioacetoacetate [from acetoacetic ester (2·7 g.), ethanol (1·2 ml.), and magnesium (0·48 g.) in ether (50 ml.)] and heated under reflux for 24 hr. Excess of dilute acetic acid was added and the separated ethereal layer was washed with sodium hydrogen carbonate solution, giving 6-methoxy-3-methylcoumarone-2-β-propionic acid (200 mg.) on acidification.

Recovery of the ethereal solution gave an orange oil (4·2 g.) which was chromatographed in benzene on alumina (pH 4; 15 × 1 cm.). Elution with the same solvent removed: (i) a narrow highly fluorescent band giving a colourless oil (90 mg.) on recovery, and (ii) a greenish-red fluorescent band giving a pale orange oil (3·1 g.). Product (i) was crystallised from light petroleum and from methanol giving plates (60 mg.), m. p. 51—52°, of *ethyl 6-methoxy-3-methylcoumarone-2-β-propionate* (VIII; R = R′ = H, R″ = $[CH_2]_2{\cdot}CO_2Et$), identical (mixed m. p. and infrared spectrum) with material obtained by esterification of the free acid (Found: C, 68·3; H, 7·4. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%), $\nu_{max.}$ 1737, 1624, 1594 cm.$^{-1}$. Product (ii) was heated at 100—110°/10^{-4} mm. for 4 hr. to remove acetoacetic ester; the non-volatile oil (2·2 g.) consisted essentially of the required keto-ester; it gave an intense ferric reaction in ethanol and formed a copper chelate.

Cyclisation.—(i) *Sulphuric acid.* The crude keto-ester (X; R = R′ = H) (12 g.) in concentrated sulphuric acid (25 ml.) was kept at 0° for 8 days, then worked up as described for the lower homologue (see above).

Acidification of the alkaline extract gave a flocculent yellow precipitate which decomposed to a tar on filtration. The unfiltered mixture was extracted with benzene, and the extract passed through silica (pH 6·75; 10 × 1 cm.). Elution with benzene gave 6-methoxy-3-methylcoumarone-2-β-propionic acid (600 mg.), m. p. 133—135°, identified by the infrared spectrum. Recovery of the ethereal solution gave an orange oil (4·5 g.) with an intense Ehrlich reaction. Chromatography in ether on alumina (pH 7; 15 × 1·5 cm.) and elution with ether removed, first, a narrow fluorescent band, giving ethyl 6-methoxy-3-methylcoumarone-2-β-propionate (20 mg.) on recovery, and then a pale blue-fluorescent band which, on recovery, gave a pale yellow oil (4·1 g.), with an intense Ehrlich reaction. The oil crystallised with difficulty from ethanol and on recrystallisation from aqueous ethanol gave needles (3·8 g.), m. p. 97—98°, of the *methylene ester* (XI; R = R′ = H) (Found: C, 69·6; H, 6·2. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%), $\nu_{max.}$ 1728, 1668, 1641, 1614 cm.$^{-1}$, $\lambda_{max.}$ 326, 316, 273, 260, 233, 215 mμ (log ε 4·05, 4·09, 4·18, 4·43, 4·37). The 2 : 4-*dinitrophenylhydrazone* formed orange-red plates, m. p. 182° (decomp.), from acetic acid–ethanol (Found: C, 59·3; H, 4·7; N, 10·7. $C_{25}H_{24}O_8N_4$ requires C, 59·05; H, 4·8; N, 11·0%).

(ii) *Polyphosphoric acid.* The keto-ester (1·5 g.) was mixed with polyphosphoric acid (20 g.) and kept at room temperature for 4 days. Recovery gave the methylene ester (700 mg.), the ethyl ester [VIII; R = R′ = H, R″ = $[CH_2]_2{\cdot}CO_2Et$) (30 mg.), and no acidic product. This method gave a cleaner product than (i).

Ethyl 6-Methoxy-2′-methyl-3 : 4′-dioxogris-2′-en-3′-carboxylate (XII; R = R′ = H, R″ = CO_2Et).—The above methylene ester (1 g.) in carbon tetrachloride (30 ml.) was ozonised as for the lower homologue, formaldehyde being isolated as the methone derivative. Chromatography of the product in ether on alumina gave a pale yellow gum (510 mg.) which solidified under ethanol when seeded with material recovered from attempted hydrolysis of the crude ester (see below). Recrystallisation from dilute ethanol gave the *coumaranone ester* (XII; R = R′ = H, R″ = CO_2Et) as needles, m. p. 110—111° (Found: C, 65·4; H, 5·6. $C_{18}H_{18}O_6$ requires C, 65·4; H, 5·5%), $\nu_{max.}$ 1735 (ester C=O), 1704 (coumaranone C=O), 1686 cm.$^{-1}$ (conjugated 6-ring C=O), $\lambda_{max.}$ 320, 272, 231, 208 mμ (log ε 3·95, 4·12, 4·17, 4·42). It gave an intractable red precipitate with Brady's reagent and no Ehrlich reaction.

6-Methoxy-2′-methylgris-2′-en-3 : 4′-dione (XII; R = R′ = R″ = H).—The coumaranone ester (3 g.) was heated under reflux with ethanol (300 ml.) and 2N-hydrochloric acid (350 ml.) for 4 hr. in nitrogen. Carbon dioxide (0·6 mol.) was evolved. The solution was concentrated *in vacuo*, and the aqueous residue was extracted with ether. Extraction of the ethereal solution with aqueous sodium hydrogen carbonate and recovery gave only a trace of acidic gum. Recovery from the ethereal extract gave a brown oil (1·6 g.) which was chromatographed in ether on alumina (pH 4; 10 × 1 cm.). Elution of the column with ether gave a pale blue fluorescent band, giving a pale yellow gum (1·5 g.) on recovery, and a dark blue fluorescent

band which on recovery gave the crystalline ester (XII; R = R′ = H, R″ = CO_2Et) (20 mg.).

The gum, consisting essentially of (XII; R = R′ = R″ = H), was neutral and unsaturated to permanganate but did not crystalline; it had $\nu_{max.}$ 1713 and 1667 cm.$^{-1}$ and $\lambda_{max.}$ 318, 272, 232, 209 mμ (log ε 3·98, 4·13, 4·22, 4·45). The 2 : 4-*dinitrophenylhydrazone* formed orange-red prisms, m. p. 230°, from ethyl acetate (Found: C, 57·4; H, 4·2; N, 12·6. $C_{21}H_{19}O_7N_4$ requires C, 57·5; H, 4·1; N, 12·8%).

Ethyl 2-*Acetyl*-6-*chloro*-3 : 5-*dimethoxyphenoxyacetate* (XIII; R = Et).—3-Chloro-2-hydroxy-4 : 6-dimethoxyacetophenone (46·0 g.), redistilled ethyl bromoacetate (66·4 g.), and anhydrous potassium carbonate (56·0 g.) were heated together under reflux in acetone (700 ml.) for 72 hr. Filtration and removal of acetone *in vacuo* gave a yellow oil, which was precipitated from ethanol (200 ml.) by ether, giving prisms (58 g.). Recrystallisation from ethanol gave the *ester* as needles (56·6 g.), m. p. 72° (Found: C, 53·3; H, 5·6; Cl, 11·3. $C_{14}H_{17}O_6Cl$ requires C, 53·1; H, 5·4; Cl, 11·2%), $\nu_{max.}$ 1763, 1735 (doublet; oxyacetate C=O), 1684 cm.$^{-1}$ (acetyl C=O), $\lambda_{max.}$ 305, 292, 258, 223 mμ (log ε 3·35, 3·43, 3·70, 4·21). The 2 : 4-*dinitrophenylhydrazone* formed yellow prisms, m. p. 136°, from ethyl acetate (Found: N, 11·3. $C_{20}H_{21}O_9N_4Cl$ requires N, 11·3%).

The *methyl ester* (XIII; R = Me), prepared from methyl bromoacetate as above, formed prisms, m. p. 103—104°, from methanol (Found: C, 51·7; H, 5·1; Cl, 12·0. $C_{13}H_{15}O_6Cl$ requires C, 51·6; H, 5·0; Cl, 11·7%), $\nu_{max.}$ 1760 (broad), 1680 cm.$^{-1}$, $\lambda_{max.}$ ~305, 293, 268, 233 mμ (log ε 3·35, 3·42, 3·66, 4·20).

2-*Acetyl*-6-*chloro*-3 : 5-*dimethoxyphenoxyacetic Acid* (XIII; R = H).—A solution of the above ethyl ester (47·4 g.) in ethanol (200 ml.), water (300 ml.), and sulphuric acid (14 ml.) was heated under reflux for 4 hr., diluted with water until cloudy, and kept overnight at 5°. The precipitate was washed with sodium carbonate solution; starting material (19·7 g.) remained.

Acidification of the alkaline extract gave the *acid* (XIII; R = H) (19·1 g.), needles, m. p. 144° (from benzene or water) (Found: C, 50·0; H, 4·6; OMe, 21·7%; equiv., 290. $C_{12}H_{13}O_6Cl$ requires C, 49·9; H, 4·5; 2OMe, 21·5%; *M*, 287·5), $\nu_{max.}$ 1751 (carboxyl C=O) and 1659 cm.$^{-1}$ (acetyl C=O), $\lambda_{max.}$ 301, 292, 258, 224 mμ (log ε 3·42, 3·39, 3·66, 4·19).

2-*Acetyl*-6-*chloro*-3 : 5-*dimethoxyphenoxyacetic Acid* (*Lactol Form*) (XIV; R= H).—The methyl ester (XIII; R = Me) (500 mg.) was heated under reflux with 3N-hydrochloric acid (20 ml.) for 6·5 hr. The solid product was filtered off, dissolved in warm sodium carbonate solution, treated with charcoal, filtered, and acidified at 0°, giving the *acid* (XIV; R = H) (311 mg.), m. p. 133—137°. It formed needles, m. p. 143—144°, from dilute ethanol (Found: C, 49·8; H, 4·6; Cl, 12·2. $C_{12}H_{13}O_6Cl$ requires C, 49·9; H, 4·5; Cl, 12·3%), $\nu_{max.}$ 1746 cm.$^{-1}$ (lactone C=O), $\lambda_{max.}$ 275, 240 mμ (log ε 3·09, 3·95). Mixtures with the acid (XIII; R = H) of m. p. 144° had m. p.s between 115° and 140°. A 1 : 1 mixture melted sharply at 119—120°, behaved as a pure compound, and was identical with material obtained as described below.

The methyl ester (XIII; R = Me) (1·5 g.) was heated under reflux for 4 hr. with N-hydrochloric acid (75 ml.). Recovery gave an *acid* (1·1 g.), m. p. *ca.* 115°, which formed needles (920 mg.), m. p. 119—120°, from benzene (Found: C, 49·6; H, 4·7; Cl, 13·6; OMe, 22·9%), $\nu_{max.}$ *ca.* 1749 (broad monomeric carboxyl CO and lactol CO), 1659 cm.$^{-1}$ (acetyl C=O). The ultraviolet spectrum was identical with that calculated for and determined with a 1 : 1 mixture of the two acids.

Methylation of the Isomeric Acids (XIII and XIV; R = H).—(i) A suspension of the acid (XIV; R = H) (29 mg., 1 mol.) in ether (5 ml.) was treated overnight with diazomethane (1 mol.) in ether (5 ml.). Recovery gave the *ester* (XIV; R = Me) (29·5 mg.), needles (from methanol) (24 mg.), m. p. 97° (Found: C, 51·6; H, 5·4. $C_{13}H_{15}O_6Cl$ requires C, 51·6; H, 5·0%), $\nu_{max.}$ 1742 cm.$^{-1}$, $\lambda_{max.}$ ~275, 235 mμ (log ε 3·07, 3·98). A mixture with the isomeric methyl ester (XIII; R = Me) had m. p. 78—85°.

(ii) The acid (XIII; R = H) gave the corresponding ester (XIII; R = Me), m. p. 103—104°, identical (mixed m. p., infrared and ultraviolet spectra) with the product from the methyl chloroacetate reaction.

7-*Chloro*-4 : 6-*dimethoxy*-3-*methylcoumarone* (VIII; R = Cl, R′ = OMe, R″ = H).—A mixture of 2-acetyl-6-chloro-3 : 5-dimethoxyphenoxyacetic acid (either form; 17·3 g.), fused sodium acetate (34 g.), and acetic anhydride (100 ml.) was heated under reflux until carbon dioxide evolution ceased (30 min.).

The cooled solution was diluted and made alkaline with sodium carbonate. The product (16 g.), m. p. 143—144°, was filtered off, passed through a column of alumina (pH 4; 50 g.) in benzene (3 l.), recovered, and crystallised from ethanol, giving the *coumarone* (VIII; R = Cl, R′ = OMe, R″ = H) as needles (14 g.), m. p. 148° (Found: C, 58·2; H, 5·0; Cl, 15·5; OMe, 27·6. $C_{11}H_{11}O_3Cl$ requires C, 58·3; H, 4·9; Cl, 15·6; 2OMe, 27·3%), $\nu_{max.}$ 1626, 1611, 1591 cm.$^{-1}$, $\lambda_{max.}$ 320, ~275, 263, 220, 216 mμ (log ε 2·42, 4·00, 4·19, 4·56, 4·56). The coumarone sublimed at 130°/10^{-4} mm., formed an unstable red picrate, gave no colour with alcoholic ferric chloride, formed a cherry-red solution in cold sulphuric acid, and like the 6-methoxy-analogue, did not decolorise permanganate in acetone.

Ethyl 7-Chloro-4 : 6-dimethoxy-3-methylcoumarone-2-carboxylate (VIII; R = Cl, R′ = OMe, R″ = CO_2Et).—Ethyl 2-acetyl-6-chloro-3 : 5-dimethoxyphenoxyacetate (XIII; R = Et) (15·8 g.) was heated under reflux for 1 hr. in a solution of sodium (1 g.) in ethanol (50 ml.). The cooled solution was diluted with water (750 ml.), and the *coumarone-carboxylate* (2·7 g.) was filtered off and crystallised from ethanol in needles, m. p. 172—173° (Found: C, 56·1; H, 5·1; Cl, 11·95. $C_{14}H_{15}O_5Cl$ requires C, 56·3; H, 5·1; Cl, 11·9%), $\nu_{max.}$ 1712 cm.$^{-1}$, $\lambda_{max.}$ 312, 298, 245, 230 mμ (log ε 4·32, 4·37, 4·34, 4·30). Acidification of the filtrate with dilute hydrochloric acid gave 2-acetyl-6-chloro-3 : 5-dimethoxyphenoxyacetic acid (XIII; R = H) (11·2 g.), m. p. 143°. In some experiments the acidic product consisted of the 1 : 1 mixture of (XIII and XIV; R = H).

7-Chloro-4 : 6-dimethoxy-3-methylcoumarone-2-carboxylic Acid (VIII; R = Cl, R′ = OMe, R″ = CO_2H).—The above ester (895 mg.) was warmed at 40° with sodium hydroxide (6 g.) in 50% aqueous ethanol (100 ml.) for 10 min. Dilution with ice and water and acidification afforded the *acid* (790 mg.), m. p. 283—286°. Sublimation at 150°/10^{-5} mm. gave plates, m. p. 310° (decomp.) (Found: C, 53·4; H, 4·3%; equiv., 273. $C_{12}H_{11}O_5Cl$ requires C, 53·3; H, 4·1%; *M*, 271), $\nu_{max.}$ 1671 cm.$^{-1}$, $\lambda_{max.}$ 293, 238 mμ (log ε 4·26, 4·31).

The *methyl ester*, prepared with diazomethane, crystallised from methanol in plates, m. p. 196° (Found: C, 54·4; H, 4·6; OMe, 33·0. $C_{13}H_{13}O_5Cl$ requires C, 54·85; H, 4·6; 3OMe, 32·7%), $\nu_{max.}$ 1713 cm.$^{-1}$. Hydrolysis of the ester (600 mg.) for 30 min. at 60° with sodium hydroxide (3 g.) in 1 : 1 aqueous ethanol (50 ml.) regenerated the free acid (500 mg.). Treatment of the acid chloride, obtained from the carboxylic acid and thionyl chloride in pyridine as an orange gum, with ethereal diazomethane yielded the *diazo-ketone* (VIII; R = Cl, R′ = OMe, R″ = $CO{\cdot}CHN_2$) which formed pale yellow needles, m. p. 118—120°, from ether (Found: C, 52·6; H, 3·6; N, 9·6. $C_{13}H_{11}O_4N_2Cl$ requires C, 53·0; H, 3·8; N, 9·5%).

Attempted Wolff rearrangement of the diazo-ketone (600 mg.) by the method used previously gave only 7-chloro-4 : 6-dimethoxy-3-methylcoumarone-2-carboxylic acid (VIII; R = Cl, R′ = OMe, R″ = CO_2H) (530 mg.), m. p. 250—260° (decomp.).

Heating the acid (200 mg.) in quinoline (0·5 ml.) with copper bronze (100 mg.) at 190—195° for 5 min., followed by recovery of the product in ether, gave 7-chloro-4 : 6-dimethoxy-3-methylcoumarone (150 mg.), m. p. 143°, identical (mixed m. p. and infrared spectrum) with material prepared above.

7-Chloro-2-formyl-4 : 6-dimethoxy-3-methylcoumarone (VIII; R = Cl, R′ = OMe, R″ = CHO).—Anhydrous hydrogen cyanide (200 ml.) was added to a solution of 7-chloro-4 : 6-dimethoxy-3-methylcoumarone (142 g.) in ether (6 l.) at 0°. A fast stream of dry hydrogen chloride was passed into the mixture at 0—5° until absorption ceased (6 hr.). The solution was kept at 0° overnight; the green aldimine hydrochloride was filtered off, washed with ether, and hydrolysed with water (10 l.) at 100°. Filtration gave the *aldehyde* (110 g.), m. p. *ca.* 140°. After 24 hr. a second crop of the aldimine hydrochloride separated from the ethereal mother-liquors, giving a further 27 g. of aldehyde on hydrolysis. The yellow colour was removed by passing a benzene solution of the aldehyde through alumina (pH 4; 60 × 2 cm.), and the product was crystallised from benzene, ethanol, or acetone. Sublimation at 130°/10^{-4} mm. and recrystallisation from acetone gave prisms, m. p. 183° (Found: C, 56·7; H, 4·45; Cl, 13·7; OMe, 24·15. $C_{12}H_{11}O_4Cl$ requires C, 56·6; H, 4·45; Cl, 14·9; 2OMe, 24·35%), $\nu_{max.}$ 1662 cm.$^{-1}$, $\lambda_{max.}$ 341, 312, 253 mμ (log ε 4·24, 4·16, 4·28). The 2 : 4-*dinitrophenylhydrazone* formed crimson plates, m. p. 312°, from acetone (Found: C, 49·4; H, 3·7; N, 12·8. $C_{18}H_{15}O_7N_4Cl$ requires C, 49·7; H, 3·5; N, 12·9%).

The *azlactone*, prepared by the method of Foster *et al.*,[6] formed crimson needles, m. p. 235°, from ethyl acetate (Found: C, 63·0; H, 4·3; N, 3·5; Cl, 8·7. $C_{21}H_{16}O_5NCl$ requires C, 63·3; H, 4·0; N, 3·5; Cl, 8·9%). Alkaline hydrolysis of the azlactone gave, after clearing with

sulphur dioxide and acidification, not the expected pyruvic acid, but *7-chloro-4 : 6-dimethoxy-2 : 3-dimethylcoumarone* (VIII; R = Cl, R′ = OMe, R″ = Me), which formed plates, m. p. 290°, from methanol (Found: C, 59·6; H, 5·2; OMe, 25·3. $C_{12}H_{13}O_3Cl$ requires C, 59·9; H, 5·45; 2OMe, 25·7%), $\nu_{max.}$ 1621 (aromatic) and 1596 cm.$^{-1}$ (C=C). Oxidation of the aldehyde with potassium permanganate in aqueous acetone gave 7-chloro-4 : 6-dimethoxy-3-methylcoumarone-2-carboxylic acid (VIII; R = Cl, R′ = OMe, R″ = CO_2H), m. p. 310° (decomp.), identical (infrared spectrum) with the acid obtained by hydrolysis of the ethyl ester.

7-Chloro-4 : 6-dimethoxy-3-methylcoumarone-2-β-propionic Acid (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2H$).—(i) The above coumarone (2·26 g., 1 mol.) and β-propiolactone (720 mg., 1 mol.) were heated together under reflux for 4 hr. The cake formed on cooling was dissolved in ether (200 ml.); the solution was filtered and extracted with sodium carbonate solution. Acidification of the extract gave a brown acidic product (720 mg.), m. p. 118—128°, which was chromatographed on silica (10 g.; pH 7) in benzene, giving a cleaner product (630 mg.), m. p. 119—130°, raised to 123—130° by recovery from the silver salt.

An ethereal solution of a sample of the acid with diazomethane gave the *methyl ester* which formed prisms, m. p. 102°, from methanol (Found: C, 57·9; H, 5·6. $C_{15}H_{17}O_5Cl$ requires C, 57·6; H, 5·5%), $\nu_{max.}$ 1739 cm.$^{-1}$ (ester C=O), $\lambda_{max.}$ 320, 294, 278, 265, 226, 223, 219 mμ (log ε 2·61, 3·30, 4·05, 4·27, 4·53, 4·52, 4·52). The remaining acid (500 mg.) was methylated as above and chromatographed in benzene on alumina (pH 4; 10 × 1 cm.). Elution of the pale-blue-fluorescent band with ether gave the pale yellow ester (350 mg.). Hydrolysis with N-ethanolic hydrochloric acid regenerated the acid as pale brown plates. Sublimation at 120—125°/10^{-4} mm. and recrystallisation from aqueous ethanol gave the *acid* as prisms, m. p. 134—135° (Found: C, 56·2; H, 5·1; Cl, 11·9%; equiv., 293. $C_{14}H_{15}O_5Cl$ requires C, 56·3; H, 5·1; Cl, 11·9%; *M*, 299), $\nu_{max.}$ (Nujol " mull ") doublet, 1722, 1706 cm.$^{-1}$; (in $CHCl_3$) 1716 cm.$^{-1}$.

(ii) *Through 7-chloro-4 : 6-dimethoxy-3-methylcoumarone-2-acrylic Acid* (VIII; R = Cl, R′ = OMe, R″ = $CH{:}CH{\cdot}CO_2H$).—A mixture of 7-chloro-2-formyl-4 : 6-dimethoxy-3-methylcoumarone (4 g.), malonic acid (6·7 g.), piperidine (330 mg.), and pyridine (17 ml.) was heated at 100° for 1 hr., and at 120° for 10 min. Acidification of the cooled solution gave a precipitate (6·1 g.; m. p. 230—240°), extraction of which with sodium carbonate solution left a residue of 7-chloro-4 : 6-dimethoxy-3-methylcoumarone (1·3 g.). Acidification of the alkaline extract precipitated the *acrylic acid* (4·75 g.), m. p. 243—247°, which formed yellow needles, m. p. 252°, from benzene (Found: C, 56·9; H, 4·6; Cl, 11·9. $C_{14}H_{13}O_5Cl$ requires C, 56·7; H, 4·4; Cl, 11·95%), $\nu_{max.}$ 1692, 1676 cm.$^{-1}$ (doublet) (this acid was insoluble in the solvents used for infrared spectra in this region), $\lambda_{max.}$ 329, 255 mμ (log ε 4·44, 4·04).

The *methyl ester*, prepared with methanolic sulphuric acid or with diazomethane in benzene followed by chromatography, formed prisms, m. p. 179°, from methanol (Found: C, 57·8; H, 5·1; OMe, 29·5. $C_{15}H_{15}O_5Cl$ requires C, 57·95; H, 4·9; 3OMe, 29·9%), $\nu_{max.}$ 1709 cm.$^{-1}$.

Reduction of the Acrylic Acid.—(*a*) The once crystallised acid (102 mg.) in acetic acid (50 ml.) was added to a suspension of Raney nickel (*ca.* 0·2 g.) in ethanol (2 ml.) and hydrogenated at room temperature and pressure until absorption ceased (1 mol. in 8 hr.). Filtration gave a green solution which was concentrated to *ca.* 5 ml. *in vacuo*. Water (100 ml.) was added and, after storage at 5° overnight, the pink solid (60 mg.), m. p. >360°, was collected. It was stirred with cold dilute hydrochloric acid for 1 hr., and the mixture filtered, giving a pale yellow acid (35 mg.), m. p. 90—95°. Purification through the sodium salt and crystallisation from light petroleum (b. p. 60—80°) gave 7-chloro-4 : 6-dimethoxy-3-methylcoumarone-2-β-propionic acid, identical (mixed m. p. and infrared spectrum) with the product obtained by method (i).

(*b*) A solution of the crude acrylic acid (93 g.) in 0·1N-sodium hydroxide (3·5 l.) was hydrogenated at room temperature and pressure in the presence of 5% palladium–strontium carbonate (50 g.). Absorption ceased after 8 hr. (0·64 mol.). Charcoal (10 g.) was added and the filtered solution was acidified, giving a pale brown solid (38 g.) and sticky material which was reprecipitated from sodium hydroxide solution, giving more product (5 g.). The product was chromatographed in benzene on silica (pH 7; 20 × 1·5 cm.), giving the acid (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2H$) (39 g.), m. p. 133—135°, identical (mixed m. p. and infrared spectrum) with material obtained as described above.

(*c*) A solution of the pure acrylic acid (56 g.; m. p. 252°) in 0·1N-sodium hydroxide (2·3 l.) was hydrogenated as in (*b*). Absorption (2 mol.) was complete in 1 hr. Extraction of the acidified solution with ether and with chloroform and recovery from the extracts gave intractable solids, m. p. 88—95° (42 g.) and 82—87° (7·8 g.) severally. Methylation of the combined

products with ethereal diazomethane gave a pale yellow oil (50·7 g.), which was chromatographed in benzene on alumina (30 × 2·5 cm.). The single bright blue band was fractionally eluted with benzene, giving as main fractions colourless needles (6·3 g.), m. p. 104—106°, from benzene–light petroleum (b. p. 60—80°), and colourless prisms (A) (3·6 g.), m. p. 98—100°, from methanol. Further elution gave colourless gums (37 g.) (B).

The needles crystallised from methanol as prisms, m. p. 107—108°, of *methyl 7-chloro-4 : 6-dimethoxy-3-methylcoumaran-2-β-propionate* (XV; R = Cl, R′ = Me) (Found: C, 57·0; H, 6·2; Cl, 11·5. $C_{15}H_{19}O_5Cl$ requires C, 57·2; H, 6·1; Cl, 11·25%), $\nu_{max.}$ 1731 cm.$^{-1}$.

Hydrolysis of the above ester (203 mg.) with boiling N-sodium hydroxide (1·5 hr.) gave laths (190 mg.), m. p. 147—148°, of *7-chloro-4 : 6-dimethoxy-3-methylcoumaran-2-β-propionic acid* (XV; R = Cl, R′ = H) (Found: C, 55·7; H, 5·7; Cl, 11·4; OMe, 20·9. $C_{14}H_{17}O_5Cl$ requires C, 55·9; H, 5·7; Cl, 11·8; 2OMe, 20·6%), $\nu_{max.}$ 1716 cm.$^{-1}$.

The material (A) recrystallised from methanol in prisms (2·7 g.), m. p. 102°, identical (mixed m. p. and infrared spectrum) with methyl 7-chloro-4 : 6-dimethoxy-3-methylcoumarone-2-β-propionate (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2Me$). Alkaline hydrolysis as above gave the corresponding acid (1·9 g.). Material (B) gave an intense blue colour with nitric acid. It was rechromatographed and the single band was eluted in 10 equal fractions with benzene; fractions 2 and 8 were again chromatographed. Fraction 2 gave an uncrystallisable gum consisting essentially of *methyl 4 : 6-dimethoxy-3-methylcoumaran-2-β-propionate* (XV; R = H, R′ = Me) (Found: C, 64·1; H, 7·0; OMe, 32·8. $C_{15}H_{20}O_5$ requires C, 64·25; H, 7·2; 3OMe, 33·2%), $\nu_{max.}$ 1728 cm.$^{-1}$. Hydrolysis as above yielded *4 : 6-dimethoxy-3-methylcoumaran-2-β-propionic acid* (XV; R = R′ = H) as prisms, m. p. 114°, from ether–light petroleum (1 : 1) (Found: C, 63·2; H, 6·8; OMe, 21·8%; equiv., 265. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8; 2OMe, 23·3%; *M*, 266), $\nu_{max.}$ 1716 cm.$^{-1}$.

Material from fraction 8 was hydrolysed as described above, giving a product which crystallised from 1 : 1 ether–light petroleum. Hand-picking of crystals followed by recrystallisation gave *4 : 6-dimethoxy-3-methylcoumarone-2-β-propionic acid* (VIII; R = H, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2H$), m. p. 124° (Found: C, 63·5; H, 5·9; OMe, 22·9. $C_{14}H_{16}O_5$ requires C, 63·6; H, 6·05; 2OMe, 23·5%).

When pyridine was added in increments of 0·5% to the pure acrylic acid before reduction, the catalyst was poisoned before dechlorination could be eliminated.

When <1% of piperidine was added, dechlorination and reduction to coumarans was inhibited, but reduction was incomplete, giving the acid (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2H$) (40%) and some starting material.

Dehydrogenation.—(i) The coumaran acid (XV; R = R′ = H) (2 g.) was heated with sulphur (200 mg.) at 220° for 20 min. and at 280° for 5 min. Continuous extraction of the gummy black acidic fraction with light petroleum followed by hand-picking of the crystallised extract gave starting material (320 mg.), m. p. 110—112°, and the required coumarone-propionic acid (VIII; R = H, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2H$) (540 mg.), m. p. and mixed m. p. 124°.

(ii) The gummy coumaran ester (XV; R = H, R′ = Me) (157 mg.) and *o*-chloranil (135 mg.) in chloroform (5 ml.) were stored in the dark for 1·5 hr. The recovered product in benzene was passed through a column of alumina (10 × 0·7 cm.), and the pale blue band eluted with benzene, giving a colourless glass (135 mg.) which formed prisms (115 mg.), m. p. 115—117°, from 1 : 1 ether–light petroleum. Further recrystallisation from methanol raised the m. p. of the *coumarone–tetrachlorocatechol complex* to 117° (Found: C, 48·15; H, 3·7; Cl, 26·85; OMe, 18·6. $C_{15}H_{17}O_5Cl,C_6H_2O_2Cl_4$ requires C, 48·0; H, 3·7; Cl, 27·1; 3OMe, 17·7%). Alkaline hydrolysis of the complex gave an acidic gum, which formed plates of the coumarone-propionic acid (VIII; R = H, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2H$), m. p. 122—124° (from 1 : 1 ether–light petroleum).

Ethyl α-Acetyl-β-oxo-7-chloro-4 : 6-dimethoxy-3-methylcoumarone-2-γ-valerate (X; R = Cl, R′ = OMe).—A solution of 7-chloro-4 : 6-dimethoxy-3-methylcoumarone-2-β-propionic acid (23·5 g.) in dry chloroform (500 ml.) was treated with phosphorus pentachloride (20 g.) and heated under reflux for 0·5 hr. Volatile products were removed at 30° *in vacuo* and the residue kept at 12 mm. for 4 hr. Ethyl ethoxymagnesioacetoacetate (12 g.) was added to a solution of the residue in ether (1·5 l.), and the mixture was boiled for 24 hr. 40% Acetic acid (250 ml.) was added and the ethereal layer was washed with sodium carbonate solution, from which the propionic acid (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2{\cdot}CO_2H$) (5·9 g.) was obtained.

Recovery of the ethereal solution gave a fluorescent orange oil (25 g.) which was chromatographed in ether on alumina (15 × 1·5 cm.) and gave the following bands on elution, first, a bright blue-fluorescing band giving the ester (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2$·CO_2Et) (800 mg.) as rosettes, m. p. 74—76°, from ethanol, and then an orange-red band with intense green fluorescence, giving an orange oil (18 g.). Heating at 110°/10^{-4} mm. for 2 hr. removed excess of ethyl acetoacetate, leaving a gum (14 g.), $\nu_{max.}$ 1737, 1718, 1621, 1600 $cm.^{-1}$, which gave a cherry-red colour with ethanolic ferric chloride and formed no stable ketonic derivatives. The gum (12 g.) in ether (100 ml.), when shaken with saturated aqueous copper acetate, deposited blue crystals (2·8 g.), m. p. 159—162°. These, combined with a further 6 g. obtained as below, crystallised from chloroform in pale blue prisms, m. p. 164°, of the *α-copper derivative* of the required keto-ester (X; R = Cl, R′ = OMe) [Found: C, 54·0; H, 5·2; Cl, 8·2. $(C_{20}H_{22}O_7Cl)_2Cu$ requires C, 54·3; H, 5·0; Cl, 8·05%].

Evaporation of the ether layer gave a green gum which was fractionally crystallised from methanol, giving the α-chelate (6 g., see above) and the β-*derivative* (1·8 g.) as green prisms, m. p. 98—100° (from ethanol) (Found: C, 54·1; H, 5·1; Cl, 7·85%). On continued heating at 120—130° it was converted into the α-isomer.

Ethyl 7-Chloro-4 : 6-dimethoxy-2′-methyl-3-methylene-4′-oxogris-2′-en-3′-carboxylate (XI; R = Cl, R′ = OMe).—(*a*) A mixture of the β-copper derivative (1·4 g.) and polyphosphoric acid (20 g.) was kept at room temperature for 10 days, diluted with ice and water (50 ml.), and extracted with ether. The dried ethereal extract was washed with sodium carbonate solution, then evaporated to a brown gum (1·18 g.). The gum was chromatographed in benzene on alumina (16 × 1·5 cm.), and the column was eluted with benzene, giving the following fluorescent bands: (i) A narrow blue band, giving ethyl 7-chloro-4 : 6-dimethoxy-3-methylcoumarone-2-β-propionate (5 mg.), m. p. 72—73°, on recovery. (ii) A greenish-blue band, giving a yellow gum; when this was kept in ethanol pale yellow rosettes (175 mg.), m. p. 137°, separated. (iii) A blue band; the yellow gum recovered from it partly crystallised when kept with light petroleum, giving rosettes (278 mg.), m. p. 129—131°.

Products (ii) and (iii) were recrystallised from ethanol, giving rosettes (410 mg.). Sublimation (120—130°/10^{-4} mm.) and recrystallisation from methanol gave needles, m. p. 137°, of the *methylene ester* (Found: C, 60·9; H, 5·3; OMe, 21·65; Cl, 8·9. $C_{20}H_{21}O_6Cl$ requires C, 61·1; H, 5·4; OAlk as OMe, 21·05; Cl, 9·0%), $\nu_{max.}$ 1731 (ester C=O), 1680 (conjugated *cyclo*hexenone C=O), 1638 (=CH_2), 1610 $cm.^{-1}$ (aromatic ring), $\lambda_{max.}$ 282, ~275, and 253 mμ (log ε 4·30, 4·28, 4·57). The ester gave a very intense blue Ehrlich reaction and decolorised permanganate.

(*b*) The α-copper derivative (500 mg.) and polyphosphoric acid (20 g.) were heated at 70—80° for 1 hr. Recovery as described above gave the required methylene ester (210 mg.), m. p. 137°.

(*c*) A mixture of the α-derivative (1·8 g.) and polyphosphoric acid (30 g.) was kept at room temperature for 10 days and worked up as above. Acidification of the alkaline extract gave the coumarone-2-β-propionic acid (600 mg.). No methylene ester was formed (negative Ehrlich test), and some copper derivative (600 mg.) was regenerated by shaking the acid with aqueous cupric acetate. Chromatography of the remaining gum (320 mg.) gave the ethyl coumarone-2-β-propionate (120 mg.) and a trace of an unidentified compound (5 mg.), m. p. 181—182° (after 2 recrystallisations from methanol) (Found: C, 61·1; H, 5·7. $C_{15}H_{17}O_4Cl$ requires C, 60·7; H, 5·8%). Infrared maxima at 1713, 1640, and 1614 $cm.^{-1}$ support its assignment as *7-chloro-4 : 6-dimethoxy-3-methyl-2-3′-oxobutylcoumarone* (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2$·COMe).

Attempted cyclisation of the crude free keto-ester (1·0 g.) with polyphosphoric acid (10 g.) at room temperature for 1 hr. and then at 70—80° for 3 min. gave the acid (VIII; R = Cl, R′ = OMe, R″ = $[CH_2]_2$·CO_2H) (900 mg.) as the only isolable product. Similar results were obtained at room temperature (24 hr.) and at 80° (0·5 hr.).

7-Chloro-4 : 6-dimethoxy-2′-methylgris-2′-en-3 : 4′-dione (XII; R = Cl, R′ = OMe, R″ = H).—(*a*) The above methylene ester (248 mg.) in carbon tetrachloride (15 ml.) was ozonised for 8 min. at room temperature (ozone output *ca.* 4 mg./min.). Solvent was removed *in vacuo*, and the residue in ether (20 ml.) and acetic acid (10 ml.) was cooled in ice during the addition of water (2 ml.) and zinc dust (100 mg.). After 12 hr., water (20 ml.) was added, and the ether layer was separated, combined with ether-washings of the aqueous layer, and extracted with sodium hydrogen carbonate solution.

The gum recovered from the ethereal extract was chromatographed in benzene on alumina (15 × 0·8 cm.). Elution gave the following fluorescent bands: (i) A lower pale blue band

which was eluted with benzene, giving starting material (12 mg.), m. p. 134—136°. (ii) A blue band; elution with benzene–methanol (100 : 1) gave a gum which crystallised from methanol in rosettes (10 mg.), m. p. 164—167°, which, recrystallised from ethanol, gave the *coumaranone* (XII; R = Cl, R′ = OMe, R″ = H) as rosettes (8 mg.), m. p. 167—168° (Found: C, 59·4; H, 4·5; Cl, 11·1. $C_{16}H_{15}O_5Cl$ requires C, 59·5; H, 4·7; Cl, 11·0%), $\nu_{max.}$ 1718 and 1683 cm.$^{-1}$, $\lambda_{max.}$ 323, 291, 235, 213 mμ (log ε 3·70, 4·30, 4·19, 4·42). (iii) A blue band, eluted with benzene–methanol (20 : 1), gave a gum which when sublimed then crystallised from methanol afforded 3-chloro-2-hydroxy-4 : 6-dimethoxyacetophenone (100 mg.). Recovery from the sodium hydrogen carbonate extract of the reaction product gave chlorine-free acidic gums (2 mg.).

(*b*) A solution of the methylene ester (137 mg.) in carbon tetrachloride was ozonised for 0·5 hr. (ozone output 0·6 mg./min.). Removal of solvent *in vacuo* gave a gum which was kept under water (25 ml.) overnight. The product was extracted with ether, and the extract was shaken with sodium hydrogen carbonate and with sodium hydroxide solution. Acidification of the alkaline extracts, and recovery, gave a chlorine-free solid (10 mg.) and 3-chloro-2-hydroxy-4 : 6-dimethoxyacetophenone (30 mg.) respectively. The gum obtained from the ethereal solution was chromatographed in benzene on alumina (20 × 0·5 cm.). Fractional elution of the broad band gave: (i) starting material (6 mg.), m. p. 134—136° (eluted by benzene). (ii) a colourless gum (27 mg.) (eluted by benzene–methanol 200 : 1), and (iii) a pale yellow gum (21 mg.) (eluted by benzene–methanol 40 : 1). Crystallisation of product (iii) gave needles (1·2 mg.), m. p. 143—149°, which were not further investigated. Product (ii) crystallised from methanol, giving rosettes (13 mg.) of *ethyl 7-chloro-4 : 6-dimethoxy-3 : 4′-dioxogris-2′-en-3′-carboxylate* (XII; R = Cl, R′ = OMe, R″ = CO_2Et), m. p. 168—171°, raised to 174° by crystallisation from ethanol (Found: C, 57·5; H, 4·9; OMe, 21·3. $C_{19}H_{19}O_7Cl$ requires C, 57·8; H, 4·85; OAlk as OMe, 20·9%), $\nu_{max.}$ 1739, 1705, 1684, 1623, 1593 cm.$^{-1}$. The ester was not hydrolysed with boiling 1—10N-hydrochloric acid, and alkaline hydrolysis caused degradation.

Reduction of 7-Chloro-4 : 6-dimethoxy-2′-methylgris-2′-en-3 : 4′-dione (XII; R = Cl, R′ = OMe, R″ = H).—The dione (10 mg.) in ethyl acetate (1 ml.) was added to a previously reduced catalyst prepared from palladium chloride (5 mg.) and charcoal (20 mg.) in water (1 ml.). The mixture was shaken in hydrogen at room temperature and pressure for 6 hr. (absorption complete in 3 hr.). The recovered gum (9 mg.) in benzene (0·5 ml.) was chromatographed on alumina (20 × 0·2 cm.). Elution of the column removed the following fluorescent bands (eluant in parentheses): (i) a bright blue forerun (benzene); (ii) a darker blue band (ether); (iii) a top bright blue band (benzene–methanol, 50 : 1). The gums recovered from each fraction were chromatographed on circular papers (Whatman No. 1). The spot containing fraction (i) was developed with ether–methanol (1 : 1), giving an inner stationary ring and a mobile outer ring. The latter was cut from the paper in ultraviolet light and eluted with ether–methanol, giving a gum, which was crystallised twice from methanol, giving prisms (0·6 mg.), m. p. 150—154°, identical (mixed m. p. and infrared spectrum) with the racemate of (*l*,*d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3-one (II). The central spot on the paper yielded a trace of gummy alcohol (infrared spectrum).

Product (ii) was chromatographed as above. A narrow mobile outer ring was identified as the racemate of (*l*,*d*)-ketone (II) (0·5 mg.). The central spot was cut out and eluted with methanol, giving a cluster of prisms (0·9 mg.), m. p. 170—175°, of the racemate of (*d*,*d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione (III). The infrared spectrum in chloroform was identical with that of the (*d*,*d*)(*i.e.*, 2*R* : 2′*R*)-diketone (III) [13] and distinct from that of the (*l*,*d*)(*i.e.*, 2*S* : 2′*R*)-form.[13]

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Akers Research Laboratories, Imperial Chemical Industries Limited,
The Frythe, Welwyn, Herts. [*Received, January 13th*, 1959.]

441. *Charge-transfer Complexes and the Mechanism of Aromatic Substitution. Part I. General Theory.*

By R. D. Brown.

A mechanism of aromatic substitution is proposed. It involves unsymmetrical charge-transfer complexes as stable intermediates and accounts for all of the features of electrophilic substitution reactions. The geometry of the unsymmetrical complexes is elucidated from quantum-mechanical considerations using a " configuration-interaction " method. Formulæ for the activation energy are deduced; they include parameters characterising the particular electrophil involved in the reaction and form a basis for a quantitative molecular-orbital treatment of relative reactivities of aromatic compounds and the orientation of substitution in such compounds.

ELECTROPHILIC aromatic substitution was until recently believed to proceed by way of a simple transition state (I), the electrophil,* E^+, approaching the aromatic compound ArH somewhat to one side of the conjugated plane, the hydrogen atom on the carbon atom undergoing substitution being synchronously dislodged and moving away on the opposite side of the conjugated plane. The potential energy was imagined to pass through a simple maximum, corresponding to the configuration (I), along the reaction co-ordinate as shown in Fig. 1. This simple picture has recently been modified in an attempt to account for certain features of electrophilic substitution reactions. One school of thought,[1,2,3,4] in order to account for kinetic isotope effects, has suggested that (I) represents an unstable intermediate:

(I)

$$ArH + E^+ \rightleftharpoons ArHE^+$$
$$ArHE^+ + B \longrightarrow ArE + BH^+ \quad \ldots\ldots\ldots\ldots (1)$$

where B is a base. This formulation was originally proposed by Lapworth [5] and has since been supported by the isolation or detection of intermediates analogous to (I).[6-12] However it will be shown that it does not satisfactorily account for all features of substitution reactions.

The variation of rates of de-deuteration with acidity of the strongly acidic media employed led another group [13,14] to propose a more elaborate mechanism:

$$Ar{-}D + H^+ \rightleftharpoons \begin{matrix} H^+ \\ \vdots \\ Ar{-}D \end{matrix} \quad \ldots\ldots\ldots\ldots (2a)$$

$$\begin{matrix} H^+ \\ \vdots \\ Ar{-}D \end{matrix} \rightleftharpoons \begin{matrix} Ar{-}H \\ \vdots \\ D^+ \end{matrix} \quad \ldots\ldots\ldots\ldots (2b)$$

$$\begin{matrix} Ar{-}H \\ \vdots \\ D^+ + B \end{matrix} \rightleftharpoons Ar{-}H + BD^+ \quad \ldots\ldots\ldots\ldots (2c)$$

* We initially consider only the most common case of an electrophil having unit positive charge.

[1] Melander, *Arkiv Kemi*, 1950, **2**, 213.
[2] Nelson, *J. Org. Chem.*, 1956, **21**, 145.
[3] Dewar, *Record Chem. Progress*, 1958, **19**, 1.
[4] Zollinger, *Angew. Chem.*, 1958, **70**, 204.
[5] Lapworth, *J.*, 1901, **80**, 1265.
[6] Pfeiffer and Wizinger, *Annalen*, 1928, **461**, 132.
[7] Kohler and Scheibe, *Z. anorg. Chem.*, 1956, **285**, 221.
[8] H. C. Brown and Pearsall, *J. Amer. Chem. Soc.*, 1952, **74**, 192.
[9] H. C. Brown and Brady, *J. Amer. Chem. Soc.*, 1952, **74**, 3570.
[10] Olah, Kuhn, and Olah, *J.*, 1957, 2174.
[11] Chopard-dit-Jean, Heilbronner, Plattner, and Weber, *Helv. Chim. Acta*, 1952, **35**, 1036, 2170.
[12] Cannell, *J. Amer. Chem. Soc.*, 1957, **79**, 2927.
[13] Gold and Satchell, *J.*, 1955, 3609, 3619; 1956, 1635, 2743.
[14] Satchell, *J.*, 1958, 1927.

in which there is a pre-equilibrium (2*a*) involving the formation of an outer complex,[7] *i.e.*, one in which only slight charge transfer to the electrophil occurs. In this mechanism the rate-determining step is (2*b*) in which the transition state corresponds to (I).

Mechanism (2) is also unsatisfactory as a general mechanism of aromatic electrophilic substitution and we suggest a new mechanism, involving unsymmetrical *charge-transfer complexes* (or inner complexes),[15] which appears to embrace all features of the reaction. It will be convenient first to summarise the significant experimental features:

(i) No kinetic hydrogen isotope effect can be detected in the nitration and bromination of aromatic compounds such as nitrobenzene or naphthalene [1] but an isotope effect is observed in the sulphonation of bromobenzene,[16] in the coupling of diazonium compounds with 7-hydroxynaphthalene-1 : 3-disulphonic acid,[4] and in the iodination of phenol.[17]

(ii) The logarithm of the rate of de-deuteration of benzene derivatives varies linearly with Hammett's acidity function H_0.[13,14,18]

(iii) Diazonium coupling of 7-hydroxynaphthalene-1 : 3-disulphonic acid is subject to general base catalysis.[4]

(iv) Electrophilic substitution is observed when the electron affinity of the electrophil is greater than the ionisation potential of the aromatic compound, *i.e.*, when $\Delta = A - I$ is positive, and it is not observed when Δ is negative.[10]

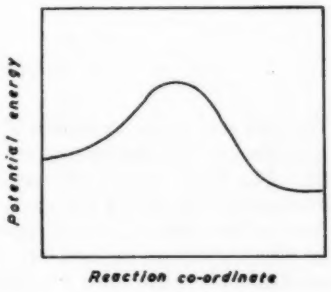


FIG. 1.

(v) Electrophilic substitution and oxidation of aromatic hydrocarbons show strong similarities, especially with respect to orientation of products.[20]

(vi) Intermediates can sometimes be isolated or detected in other ways.

Critique of Previous Mechanisms.—The simplest mechanism, represented by Fig. 1, fails to account for the observations (i), (ii), (iii), and (iv). It therefore calls for no further detailed appraisal.

Mechanism (1) can account for both (i) and (iii), as has been demonstrated by Zollinger.[4] Observation (vi) also fits neatly into this mechanism. However since the second step is a bimolecular reaction with a base it is not possible to account for (ii) because, according to the Zucker–Hammett principle,[21,22] this observation implies that the transition state resembles the conjugate acid of the substrate. It was for this reason that mechanism (2) was proposed.

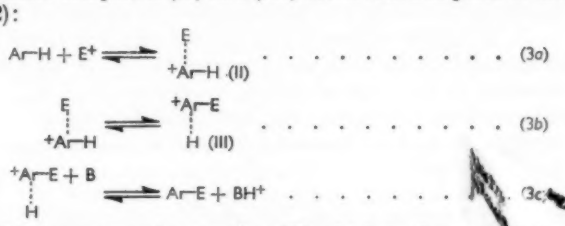
Mechanism (2) accounts for the observation (ii). No explanation of observations (iv) and (v) emerges but at first sight it does seem possible to account for observations (i) and (iii). Thus if the first step could be rate-determining no kinetic isotope effect would be observed; if (2*c*) could be rate-determining then base catalysis would be understandable. However neither the first nor the third stage of mechanism (2) can become rate-determining because the formation or dissociation of an outer complex requires little activation energy.[15]

The suggestion that a charge-transfer complex is involved in electrophilic substitution was made by Nagakura and Tanaka [19] on the basis of observation (iv) but they did not develop this in the light of the other features of substitution reactions. Others [9,23] have

[15] Mulliken, *J. Phys. Chem.*, 1952, **56**, 801.
[16] Berglund-Laesson and Melander, *Arkiv Kemi*, 1953, **6**, 219.
[17] Grovenstein and Kilby, *J. Amer. Chem. Soc.*, 1957, **79**, 2973.
[18] Mackor, Smit, and van der Waals, *Trans. Faraday Soc.*, 1957, **53**, 1309.
[19] Nagakura and Tanaka, *J. Chem. Phys.*, 1954, **22**, 563.
[20] Waters, *J.*, 1948, 727.
[21] Zucker and Hammett, *J. Amer. Chem. Soc.*, 1939, **61**, 2791.
[22] Long, *Proc. Chem. Soc.*, 1957, 220.
[23] Muller, Pickett, and Mulliken, *J. Amer. Chem. Soc.*, 1954, **76**, 4770.

regarded charge-transfer, or inner, or σ-complexes as intermediates, but with an assumed geometry analogous to (I), and it has just been seen that this simple picture cannot be reconciled with all the observations.

The Charge-transfer Complex Mechanism.—The mechanism now suggested to correlate the observations on electrophilic substitution is the following, differing from mechanism (2) in that unsymmetrical charge-transfer complexes (II) and (III) are invoked in place of the outer complexes formulated in (2):



The first step is the formation of a charge-transfer complex (II) which in the second step isomerises to the charge-transfer complex (III) by way of a transition state analogous to (I). The final step is the base-catalysed loss of a proton from (III). In contrast to mechanism (2), any of the steps of (3) may be rate-determining because, as discussed in detail below, they all involve appreciable activation energies. It is thus possible to account for observations (i), (ii), and (iii). The observation (iv) is readily explained by the proposed mechanism because when Δ is positive a charge-transfer complex will form but not when Δ is negative.* Similarities between electrophilic substitution and oxidation are understandable because the first step (3*a*) is a typical redox reaction.

The possibility that (I) represents a stable intermediate requires that the configurations (II) and (III) are separated by a potential-energy minimum instead of the maximum envisaged here. This possibility is considered more fully later.

Origin of the Potential Barriers.—One important distinction between the proposed mechanism (3) and mechanism (2) is that only for the former can appreciable potential barriers exist for the first and the third step. The origin of these barriers in mechanism (3) must now be considered. The variation in potential energy accompanying the formation of a charge-transfer complex has been discussed by Mulliken,[15] although he has not dealt with the case of interest here, *i.e.*, electrophil with unit positive charge, uncharged nucleophil, and Δ positive. It is convenient to use Mulliken's formulation of the problem—a simple form of configuration-interaction treatment in which the complex is represented as intermediate between the configuration without charge transfer, eigenfunction Ψ_0, and the configuration corresponding to the transfer of one electron from the highest occupied orbital of the nucleophil to the lowest unoccupied orbital of the electrophil, eigenfunction Ψ_1:

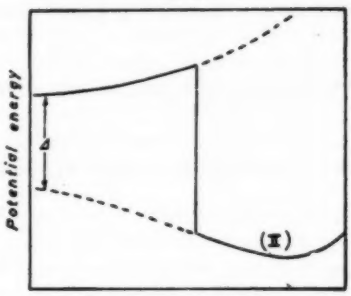
$$\Psi = a_0\Psi_0 + a_1\Psi_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

For positive Δ the separated reactants represent an *excited* state of the system because the structure E...ArH$^+$ has an energy value lower than that of the structure E$^+$...ArH by an amount Δ. As the reactants approach, the potential energy increases (in the quantum-mechanical picture of the process this is due to increasing mesomerism between Ψ_0 and Ψ_1) until at some stage an electronic transition to the ground state occurs. The process is represented by the full line in Fig. 2. The stage at which an electronic transition to the ground state occurs will depend *inter alia* on the rate at which the reactants approach one another. Eventually a minimum corresponding to (II) is reached. This description applies to reactions in vacuum or in non-polar, non-solvating solvents, conditions under which substitutions involving charged electrophils do not appear to have been observed.

* This criterion needs modification if the electrophil does not carry unit positive charge, or if the substrate is charged.

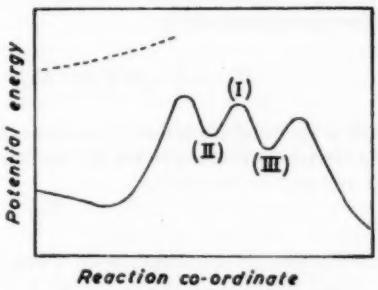
The picture is changed significantly in the presence of a solvating solvent. The electrophil is solvated, often very strongly,* and thus its effective electron affinity is considerably reduced. The potential barrier to formation of the charge-transfer complex (II) arises because in the process the electrophil has to break free from its solvation sheath or at least the sheath has to be considerably distorted to allow a close approach of the electrophil and the aromatic molecule. The activation energy may thus amount to an appreciable fraction of the solvation energy of the electrophil in the particular solvent.† Alternatively the process may be viewed as the bimolecular reaction of the aromatic compound with the charge-transfer complex formed between the electrophil and the solvent nucleophil, *i.e.*, as an electrophil-transfer reaction. It seems likely that the effective electron affinity of the

FIG. 2.



Upper curve $E^+ \ldots ArH$.
Lower curve $E \ldots ArH^+$.

FIG. 3.



Upper (broken) curve $E_{solv.} \ldots ArH^+$.
Lower curve $E^+_{solv.} \ldots ArH$.

electrophil is reduced in the solvation complex sufficiently to make Δ negative; then the separated reactants represent the ground state of the combined system. As the reactants approach one another an outer complex is formed and, as the electrophil breaks from its solvation sheath, its electron affinity steadily increases until Δ is positive and the complex then is to be regarded as a charge-transfer complex. The variation in potential energy throughout the reaction will be roughly as shown in Fig. 3.

In certain reactions, such as the Friedel–Crafts reaction, an inert solvent is used and the uncharged electrophil may be considered to be a positively charged electrophil " solvated " by an anion, *e.g.*, $R{-}AlCl_4$ may be regarded as the carbonium ion " solvated " by the $AlCl_4^-$ ion. A related reaction provides supporting evidence for this proposed mechanism of substitution. Hydrogen chloride and aromatic compounds form unstable complexes in inert solvents at −80°, little or no activation energy being involved.[9] They do not increase the conductivity of the solution and deuterium is not exchanged with the aromatic compound. These must be regarded as outer complexes of the type postulated in mechanism (2). The bare proton has an electron affinity high enough for Δ to be positive in these interactions [19] but it is so strongly " solvated " by the chloride anion that in this combination the effective Δ is negative and the potential barrier to deuterium exchange is prohibitively high. In the presence of aluminium chloride more stable complexes are formed, the solution is an electrical conductor and deuterium is exchanged with the aromatic compound. Furthermore these complexes are observed to form and dissociate slowly. They have been recognised as inner complexes, σ-complexes, or charge-

* *E.g.*, the solvation energy of a proton in water or similar solvents.

† In the case of polyatomic electrophils non-bonded repulsions between the electrophil and the aromatic compound may sometimes contribute to the activation energy. The rearrangement of the solvation sheath accompanying the formation of the activated complex will also contribute to $\Delta S^{\ddagger}$; however our primary concern in the present treatment is with the energetics of the mechanism.

transfer complexes.* Consequently it is reasonable to consider any of the steps in mechanism (3) as being the slow step, as is required to account for the observations listed above.

Quantum-mechanical Treatment.—The new mechanism leads to a fresh quantum-mechanical treatment of aromatic substitution. We shall first develop some general results. The eigenfunction of the charge-transfer complex is represented, as in eqn. (4), as a combination of two singlet electronic configurations,† Ψ'_0 and Ψ'_1, the energy of the ground state of the complex being obtained from the secular equation:

$$\begin{vmatrix} H_{00} - E & H_{01} \\ H_{01} & H_{11} - E \end{vmatrix} = 0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

in which for simplicity Ψ'_0 and Ψ'_1 have been assumed to be orthogonal and the following symbolism has been used:

$$H_{00} = \int \Psi_0 \mathscr{H} \Psi_0 d\tau; \; H_{11} = \int \Psi_1 \mathscr{H} \Psi_1 d\tau; \; H_{01} = \int \Psi_0 \mathscr{H} \Psi_1 d\tau \quad . \quad . \quad (6)$$

where $\mathscr{H}$ is the total Hamiltonian for the complex.

The electrostatic energies for the configurations $E^+ \ldots ArH$ and $E \ldots ArH^+$ will be very similar and so ‡ we may write

$$H_{00} - H_{11} = \Delta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

When Δ is positive the solution of (5) of lower energy is

$$E_1 = H_{00} - \{\Delta + (\Delta^2 + 4H_{01}^2)^{\frac{1}{2}}\}/2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Now except in special cases where Δ happens to be small, the resonance energy H_{01} for interaction of the two configurations will be small compared with Δ. In this case eqn. (8) simplifies to

$$E_1 = H_{00} - \Delta - H_{01}^2/\Delta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

This approximation more clearly reveals the main factors determining the energy of formation of the complex although in the numerical calculations reported in Part II exact formulæ equivalent to (8) have been used.

* The formation of the charge-transfer complex might be regarded as a bimolecular reaction between the electrophil $AlCl_3$ and the outer complex, the Cl^- nucleophil being transferred to the aluminium chloride to form an anion such as $AlCl_4^-$ and the " desolvated " proton remaining bound to the aromatic compound in a charge-transfer complex. The observed deuterium exchange would occur by isomerization of the complex as in step (3*b*). An alternative interpretation of the charge-transfer complex being formed by a reaction between $HAlCl_4$ and the aromatic compound must be rejected because there is no indication of any compound formation between HCl and $AlCl_3$.[24] The properties of complexes formed by interaction of HBr, $AlBr_3$, and aromatic compounds,[25] and by interaction of HF, BF_3, and aromatic compounds [26] may be interpreted similarly. It is significant that the relative stabilities of these charge-transfer complexes closely parallel the ease of electrophilic substitution in the substrates.[2,9]

† Configurations of the type $E^- \ldots ArH^{++}$ (represented by a configurational function Ψ_d, say), corresponding to a transfer of two electrons, are neglected on the grounds that the electron affinity of E is always much lower than that of E^+ and the ionization potential of ArH^+ is always much higher than that of ArH. Therefore H_{dd} would represent a higher energy than H_{00} and a considerably higher energy value than H_{11} and thus Ψ'_d will not make a significant contribution to the total eigenfunction of the complex. In special cases it may happen that Ψ'_d and Ψ'_0 have comparable energy values so that Ψ'_d may make a contribution to the total eigenfunction similar to the small contribution made by Ψ'_0 but this aspect has not been explored further in the present study.

‡ The validity of this assumption is confirmed by the success with which calculated relative rates of nitration of polycyclic hydrocarbons, reported in Part II, based on equations (8) and (15), correlate with the observed rates.

[24] Baddeley, *Quart. Rev.*, 1954, **8**, 355.
[25] H. C. Brown and Wallace, *J. Amer. Chem. Soc.*, 1953, **75**, 6268.
[26] McCauley and Lien, *J. Amer. Chem. Soc.*, 1951, **73**, 2013.

If the energy of the separated reactants is E° and we put $H_{00} - E^\circ = X$ then the energy of formation of the charge-transfer complex from the reactants *in vacuo* is *

$$\Delta E = X - \Delta - H_{01}^2/\Delta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

In the presence of a solvent a change in the solvation energy of E^+ accompanying the formation of the complex must be added to the right-hand side of (10). If the energy required to desolvate the electrophil is Y then, in the presence of a solvent:

$$\Delta E = X + Y - \Delta - H_{01}^2/\Delta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

A similar expression will apply for the activation energy for the first step:

$$\Delta E^\ddagger = X^\ddagger + Y^\ddagger - \Delta^\ddagger - H_{01}^{\ddagger 2}/\Delta^\ddagger \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

in which values of the quantities appropriate to the activated complex are indicated by ‡.

One consequence of (12) is that if solvation effects are similar for two different electrophils then the greater the value of $\Delta^\ddagger$, *i.e.*, the greater the electron affinity of the electrophil, the lower will be the first potential barrier. This may account for the fact that in the case of attack by a proton, which has a higher electron affinity than that of other common electrophils, the formation of the charge-transfer complex is not rate-determining whereas when the electrophil is NO_2^+ or Br^+, of lower electron affinity than H^+, the first step is rate-determining.

For reaction of different aromatic compounds with a given electrophil in a given solvent the greater the value of $\Delta^\ddagger$, and, to a smaller extent, the greater the value of $H_{01}^{\ddagger 2}$, the smaller is the activation energy for the first step. Thus when the first step is rate-determining the reaction is faster the lower the ionisation potential of the aromatic compound and the positions preferentially attacked are those for which $H_{01}^{\ddagger 2}$ is greatest.

The dependence of the energy of the first transition state upon $H_{01}^{\ddagger 2}$ shows that the geometry of the transition state will be that for which $H_{01}^{\ddagger 2}$ is as great as possible (limitations by non-bonded repulsions, etc., being borne in mind). According to the principle of maximum overlapping,[27] it will be that for which the lowest-energy vacant orbital of the electrophil most strongly overlaps the highest occupied molecular orbital of the aromatic compound. Every molecular orbital has a local maximum magnitude in the vicinity of each conjugated nucleus (except when this coincides with a node), as is clear when the π-orbitals are successfully represented by linear combinations of atomic $2p\pi$-orbitals. The electrophil will therefore be situated immediately above an atom of the conjugated system to obtain maximum overlap with a $2p\pi$-orbital, as shown in Fig. 4. A series of isomeric charge-transfer complexes may be pictured in which the electrophil is located above each of the conjugated atoms. If the conjugated atom has an attached hydrogen atom then the complex in which the electrophil is located in this atom may isomerise by way of an activated complex (I), E and H changing places, corresponding to the process (3*b*), and leading to a substituted product upon deprotonation. When the formation of (II) is rate-determining the proportions of isomers will be determined by the relative stabilities of the isomeric complexes (II) and so by the relative values of $H_{01}^{\ddagger 2}$ for the various positions around the conjugated system. The simple LCAO molecular-orbital theory provides a means of estimating the variation in $H_{01}^{\ddagger 2}$ and hence predicting orientations and relative reactivities of positions in aromatic compounds. This aspect is explored in detail in Part II. It may be seen however from (12) that, since the

* A term representing the increase in energy arising from non-bonded repulsions between the aromatic compound and parts of the electrophil (especially when this is polyatomic) not directly involved in the electron-transfer interaction should strictly be included in equations (10), (11), and (12). Such interactions must be assumed to be constant for a given electrophil, and independent of the aromatic compound and of the position attacked by the electrophil. Although this effect has not been explicitly considered in previous treatments of chemical reactivity, such treatments implicitly involve this assumption.

[27] Mulliken, *J. Amer. Chem. Soc.*, 1950, **72**, 4493.

greater the value of $\Delta^{\ddagger}$ the more rapid is the reaction, for rapid reactions the activation energy is less sensitive to values of H_{01}[‡2], *i.e.*, the electrophil discriminates less between the various positions of the aromatic system. In fact it will be shown in Part II that quantitative aspects of the selectivity of electrophils noticed by Brown and Nelson [28] may be deduced from eqn. (12).

Quantum-mechanical estimations of the energies of structures of the type (I) have been made by an alternative procedure [23,29,30] in which conjugation of the orbitals of the electrophil and the outgoing hydrogen with the aromatic system is treated by the LCAO molecular-orbital procedure, an antisymmetric combination of the E and H orbitals being regarded as a " pseudo-π-orbital." This type of treatment could equally well be used for the unsymmetrical complexes of type (II) but it suffers from a difficulty, noticed particularly by Fukui *et al.*,[30] that if the pseudo-orbital is assigned a Coulomb parameter greater than that of a carbon orbital, as would be assumed from the known electron affinities of typical electrophils,[19] the final π-electron density in the pseudo-orbital becomes

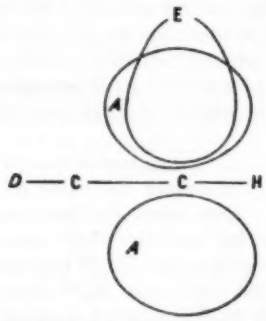


FIG. 4.
A, $2p\pi$ Orbital.
D, Conjugated plane perpendicular to paper.

considerably greater than unity. Fukui *et al.* tried to overcome this by incorporating the dependence of Coulomb parameter on π-electron density into the treatment but they did not find this feasible for numerical calculations.

The present " configuration-interaction " method overcomes this difficulty because we include only configurations with 0 or 1 electron in the electrophil-orbital, so that the electron density in this orbital cannot exceed unity. Furthermore it happens that the " configuration-interaction " treatment is particularly suited to numerical work, it being possible to develop a numerical index of reactivity corresponding to an exact solution of secular equations similar to (5) or (15). The alternative treatments are based either on idealised forms of (I) [31] or on quantities such as " superdelocalisabilities " which come from approximate solutions of secular equations. A numerical comparison of the methods is made in Part II.

Extent of Charge Transfer.—The extent of charge transfer, T, is given by the weight of the charge-transfer configurations in the eigenfunction Ψ of the complex. If Ψ is normalised then [see eqn. (4)] $T = 1 - a_0^2$. From (5) and (9) one finds

$$T \approx 1 - (H_{01}/\Delta)^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

showing that charge transfer is less complete the greater the extent of resonance interaction between the electrophil orbital and the aromatic orbital, and more nearly complete the greater the value of Δ. In the case of the nitration some values of T are estimated in Part II by use of equation (13). The values vary from almost unity in the great majority of cases to a more moderate value for exceptional aromatic compounds such as benzene ($T = 0{\cdot}75$). Thus the formulæ in equations (3), implying complete charge transfer (*i.e.*,

[28] H. C. Brown and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 6292.
[29] Fukui, Yonezawa, and Nagata, *Bull. Chem. Soc. Japan*, 1954, **27**, 423.
[30] Fukui, Yonezawa, and Nagata, *J. Chem. Phys.*, 1957, **27**, 1247.
[31] R. D. Brown, *Quart. Rev.*, 1952, **6**, 63.

$T = 1$), are an accurate representation of the charge distribution in the charge-transfer complexes.

Charge Transfer from All Occupied Orbitals.—In the preceding treatment it was supposed that the electron transfer involved only the highest occupied orbital of the aromatic compound. In some cases the highest occupied orbital is degenerate and in other cases the two highest occupied orbitals are nearly degenerate. When configurations arising from charge-transfer from degenerate uppermost filled orbitals are considered the solution of the secular equations having lowest energy is:

$$E_1 = H_{00} - \{\Delta + (\Delta^2 + 4\sum)^{\frac{1}{2}}\}/2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

where $\sum$ represents the sum of squares of resonance integrals over the degenerate orbitals:

$$\sum = \sum_j H_{0j}^2$$

When charge-transfer from the two uppermost nearly degenerate orbitals is considered a cubic equation in the energy is obtained from the secular determinant. This is considered explicitly in Part II. It is not difficult to write down the equation for the energy when configurations arising from charge-transfer from all occupied orbitals are included in the treatment. It is: [32]

$$\left[W - \sum_j \left(\frac{H_{0j}^{\ddagger 2}}{W - \Delta_j^{\ddagger}}\right)\right] \Pi_k (W - \Delta_k^{\ddagger}) = 0 \quad . \quad . \quad . \quad . \quad . \quad (15)$$

and the most positive solution corresponds to the energy of the transition state for step (3*a*) where

$$W = H_{00}^{\ddagger} - E$$
$$\Delta_j^{\ddagger} = H_{00}^{\ddagger} - H_{jj}^{\ddagger} = A^{\ddagger} - I_j$$

and I_j is the ionisation potential of the aromatic compound for ionisation from the jth occupied molecular orbital. The summations and products in (15) are taken over all occupied molecular orbitals.

The activation energy for formation of the charge-transfer complex is then given by

$$\Delta E^{\ddagger} = X^{\ddagger} + Y^{\ddagger} - W^{\circ} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

W° being the most positive solution of (15).

Intermediates Detected in Aromatic Substitution.—One of the features of aromatic substitution listed earlier [observation (vi)] was the isolation or detection of intermediates in substitution reactions. These have always been assumed to have a symmetrical structure (I), although there is no positive stereochemical evidence requiring this. The essential point of the present theory is that the charge-transfer complexes which are intermediates in the reaction have the unsymmetrical structure (II). There seems to be no difficulty in ascribing to the intermediates so far detected [6-12] unsymmetrical charge-transfer structure (II). In such structures no loss of aromaticity occurs. Furthermore in a quantum-mechanical investigation of this point Fukui *et al.*[29] showed that (I) normally corresponds to a local *maximum* in potential energy.

(V)

A possible exception might occur when the aromatic compound is an anion, such as in phenoxide. It is possible that the uncharged structure (V) is then a stable configuration owing to loss of electrostatic energy accompanying the formation of an uncharged covalent entity. However this would need to be more than enough to off-set the loss of aromaticity in such a structure.

Conclusion.—The present theory, involving unsymmetrical charge-transfer complexes, appears to account for the currently known features of aromatic electrophilic substitutions. Attention has been centred on uncharged aromatic systems and positively charged electrophils because charge transfer does not then appreciably alter the overall electrostatic properties, and hence electrostatic energy, of the interacting system. However

[32] Dewar, *Proc. Camb. Phil. Soc.*, 1949, **45**, 638.

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there is no difficulty in extending the present treatment to cases of uncharged electrophils such as SO_3, by including recognition of, for example, the dielectric properties of the solvent in facilitating the formation of an ion-pair configuration in the charge-transfer complex. In cases such as SO_3 a further interesting aspect might enter, namely that the lowest unfilled orbital of the electrophil may be sufficiently extensive to overlap simultaneously more than one $2p\pi$-orbital of the aromatic compound in the charge-transfer complex. This must inevitably happen in reactions such as ozonolysis, Diels–Alder addition, osmium tetroxide oxidation, etc., and it is hoped to extend the present treatment to these reactions in a subsequent paper. The charge-transfer complex mechanism is also applicable to nucleophilic substitution in aromatic compounds and to reactions of aromatic compounds with free radicals, as has been noted by Fukui *et al.*[29,30]

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442. *Charge-transfer Complexes and the Mechanism of Aromatic Substitution. Part II.*[1] *Molecular-orbital Calculations.*

By R. D. BROWN.

A simple molecular-orbital treatment of the mechanism of aromatic substitution developed in Part I leads to quantities termed Z-values as indices of chemical reactivities of positions in aromatic compounds. The calculations of Z-values depend upon two parameters which characterize the nature of the electrophil and the transition state in reaction. These parameters have been evaluated for nitration at 0° in acetic anhydride. The resultant Z-values for positions in polycyclic hydrocarbons show a good linear correlation with logarithms of rates of nitration, the correlation being superior to that shown by atom-localization energies or superdelocalizabilities. The orientation of substitution in some non-benzenoid hydrocarbons is also accounted for satisfactorily by Z-values. Although it is possible to calculate Z-values when charge transfer from more than one occupied orbital of the aromatic compound is considered, orbitals other than the frontier orbital scarcely alter the Z-value except when the orbital is almost degenerate with the frontier orbital.

The effect of inductive substituents on the Z-values of benzene positions is evaluated by first-order perturbation theory. The results are in agreement with observed orientations of substitution for such benzene derivatives. The quantitative selectivity relationships for electrophils observed by H. C. Brown and Nelson are explained by the present theory which predicts that the same quantitative relation should hold for all purely inductively substituted benzenes. Some calculations of Z-values for benzenes with conjugating substituents are reported. They account for the general features of orientation of substitution in these compounds.

Calculations of the extent of charge transfer in the transition state for the complexes formed in the nitration of polycyclic hydrocarbons show that it is virtually complete except in the case of benzene.

The significance of frontier-electron densities, superdelocalizabilities, π-electron densities, and atom-localization energies in the light of the charge-transfer mechanism of aromatic substitution is discussed.

IN Part I[1] a new mechanism was proposed for aromatic substitution, involving the formation of unsymmetrical charge-transfer complexes between the electrophil E^+ and the

[1] Part I, R. D. Brown, preceding paper.

aromatic compound ArH. It was possible to formulate the activation energy for formation of such complexes by using a " configuration interaction " molecular-orbital method. In the present paper it is proposed to show that a quantitative treatment of relative reactivities of different aromatic compounds, or different positions in an aromatic compound, is possible. Because of the large body of numerical data now available in the literature the simple molecular-orbital treatment is a convenient basis for the calculations.

It was shown in Part I that the activation energy for formation of the charge-transfer complex is

$$\Delta E^{\ddagger} = X^{\ddagger} + Y^{\ddagger} - W^{0} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $X^{\ddagger} = H_{00}^{\ddagger} - E^{0}$, E^{0} being the energy of the separated reactants and $H_{00}^{\ddagger}$ the energy value for the configuration $E^{+}\ldots ArH$ with the geometry of the transition state. W^{0} is the most positive solution of a secular equation and if we consider charge transfer from the highest filled molecular orbital of ArH only then

$$W^{0} = \tfrac{1}{2}\{\Delta^{\ddagger} + (\Delta^{\ddagger 2} + H_{01}^{\ddagger 2})^{\frac{1}{2}}\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

or, for $\Delta^{\ddagger 2} \gg H_{01}^{\ddagger 2}$

$$W^{0} = \Delta^{\ddagger} + H_{01}^{\ddagger 2}/\Delta^{\ddagger} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where

$$\Delta^{\ddagger} = A^{\ddagger} - I \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$A^{\ddagger}$ being the effective electron affinity of the electrophil when desolvated to the extent appropriate to the transition state, and I the ionisation potential of the aromatic compound. $H_{01}^{\ddagger}$ is the resonance integral for interaction of the singlet configurations $\Psi_0 = E^{+}\ldots ArH$ and $\Psi_1 = E\ldots ArH^{+}$ in the transition state:

$$H_{01}^{\ddagger} = \int \Psi_0^{\ddagger} \mathscr{H}^{\ddagger} \Psi_1^{\ddagger} d\tau \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The configurations are represented more explicitly by antisymmetrized products of orbital functions, or linear combinations of these:

$$\Psi_0 = \mathscr{A}[\psi_1(1)\alpha(1)\psi_1(2)\beta(2)\ldots\psi_f(n-1)\alpha(n-1)\psi_f(n)\beta(n)]$$

$$\Psi_1 = \frac{1}{\sqrt{2}}\{\mathscr{A}[\psi_1(1)\alpha(1)\psi_1(2)\beta(2)\ldots\psi_f(n-1)\alpha(n-1)\chi_e(n)\beta(n)] + \mathscr{A}[\psi_1(1)\alpha(1)\psi_1(2)\beta(2)\ldots\chi_e(n-1)\alpha(n-1)\psi_f(n)\beta(n)]\}$$

where $\mathscr{A}$ is the antisymmetrizer operator, ψ_f the frontier molecular orbital of the aromatic compound and χ_e the lowest energy vacant orbital of the electrophil.* To proceed further we shall take the Hamiltonian operator to be

$$\mathscr{H}^{\ddagger} = \sum_i \mathbf{H}_{\mathrm{eff}}^{\ddagger}(i) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where $\mathbf{H}_{\mathrm{eff}}^{\ddagger}(i)$ is a Hartree–Fock one-electron Hamiltonian operator, the summation being over all electrons sufficiently loosely bound for their transfer to the vacant electrophil orbital to be taken into consideration. In the calculations described below the transfer of an electron from some or all of the π-molecular orbitals has been considered (although the inclusion in the calculations of configurations arising from transfer from any but the highest two or three π-orbitals was found to have a negligible effect) but transfer from the σ-orbitals was neglected. Terms in the total Hamiltonian applying to electrons too firmly bound to the aromatic compound for transfer to be significant make no contribution to the

* It is assumed here that χ_e is an atomic orbital but for some electrophils it might be a more extensive molecular orbital. This makes no significant difference to our analysis [the constant $c_{p\mu}$ in eqn. (7) must then be taken to be the product of the frontier-orbital coefficient of χ_μ and the coefficient of that atomic orbital in χ_e which overlaps χ_μ] so long as χ_e appreciably overlaps only one of the $2p\pi$ orbitals of the aromatic system. For some reagents such as ozone, dienophils, etc., multiple overlapping may be an important feature in any " charge-transfer complex " mechanism for their attack on conjugated systems.

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expression for the energy of formation of the complex when the approximations described below are introduced and so have not been included in (6).

To make the calculations more manageable and to put them on a footing comparable with previous molecular-orbital treatments of chemical reactivity, the simple Hückel LCAO approximation will be invoked—the two-electron integrals occurring in the evaluation of $H_{01}^{\ddagger}$ will be neglected, it being supposed that compensation for this is achieved by empirical evaluation of one-electron integrals (the coulomb and resonance parameters of the Hückel method). The molecular orbitals of the aromatic compound will be taken to be linear combinations of $2p\pi$-atomic orbitals and overlap integrals will be neglected.

The configuration-interaction integral then reduces to

$$H_{01}^{\ddagger} = \sqrt{2}c_{f\mu}\int \chi_e \mathbf{H}_{e\pi}^{\ddagger}\chi_\mu d\tau$$
$$= \sqrt{2}c_{f\mu}\beta_{e\mu} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

$C_{f\mu}$ being the coefficient of χ_μ in the frontier orbital of ArH, χ_μ being the $2p\pi$-orbital overlapped appreciably by the electrophil orbital. The resonance integral $\beta_{e\mu}$ represents the interaction energy of the electrophil orbital χ_e and the $2p\pi$-orbital of ArH which it overlaps. It will be assumed that for a given electrophil $\beta_{e\mu}$ has the same value for any carbon atom μ whose substitution is under consideration. This is virtually equivalent to assuming that for a given electrophil the distance between it and the carbon atom to which it attaches itself is constant in all activated complexes.*

It is convenient to express $\beta_{e\mu}$ in terms of β, the standard resonance integral of a benzene bond:

$$\beta_{e\mu} = g_e^{\ddagger}\beta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

$g_e^{\ddagger}$ being a constant characteristic of the particular electrophil under consideration.

If charge transfer from orbitals other than the frontier orbital is considered the configuration-interaction treatment of the activation energy involves matrix elements of the type $H_{0j}^{\ddagger}$ and $H_{jk}^{\ddagger}$. These have the values:

$$H_{0j}^{\ddagger} = \sqrt{2}g_e c_{j\mu}^{\ddagger}\beta$$
$$H_{jk}^{\ddagger} = -\int \psi_j \mathbf{H}_{e\pi}^{\ddagger}\psi_k d\tau = 0$$

The value of W^0 in equation (1) then becomes the most positive zero of the function

$$f(W) = \left(W - 2g_e^{\ddagger 2}\beta^2 \sum_j \frac{c_{j\mu}^{\ 2}}{W - \Delta_j^{\ddagger}}\right) \Pi_k (W - \Delta_k^{\ddagger}) \quad . \quad . \quad . \quad . \quad (9)$$

It remains to express $\Delta_j^{\ddagger}$ in terms of the Hückel MO treatment of the system. The ionization potential for the jth molecular orbital of ArH is written $-e_j = -\alpha - y_j\beta$, α being the standard Coulomb integral of carbon, y_j a number calculated from the Hückel secular equations. The electron affinity of the vacant orbital χ_e of the electrophil may be written $A^{\ddagger} = -\alpha - y_e^{\ddagger}\beta$, $y_e^{\ddagger}$ being a number characteristic of the particular electrophil considered.

Then

$$\Delta_j^{\ddagger} = A^{\ddagger} - I_j$$
$$= -\beta(y_e^{\ddagger} - y_j) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$
$$= -\beta Y_j, \text{ say}, \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

where Y_j is a number, positive if $\Delta_j^{\ddagger}$ is positive. As pointed out in Part I, $\Delta_f^{\ddagger}$ is positive, *i.e.*, Y_f is positive, when electrophilic substitution occurs.

* This distance will be determined by two factors: Non-bonded repulsions will tend to keep the electrophil and the aromatic compound from approaching one another too closely but, subject to this, the more extensively χ_e and χ_μ overlap, the more stable the complex will be.

If (11) is substituted in (9) and we write $W = -\beta Z$ then the value of W^0 is obtained from the most positive zero of the function

$$F(Z) = \left(Z - 2g_e^{\ddagger 2}\sum_j \frac{c_{j\mu}^2}{Z - Y_j}\right)\Pi_k(Z - Y_k) \quad . \quad . \quad . \quad . \quad . \quad (12)$$

Equations (2) and (3) similarly simplify to

$$Z^0 = -W^0/\beta = [Y + (Y^2 + 2g_e^{\ddagger 2}c_\mu^2)^{\frac{1}{2}}]/2 \quad . \quad . \quad . \quad . \quad (13)$$

and

$$Z^0 = Y + 2g_e^{\ddagger 2}c_\mu^2/Y \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

the quantities Y and c_μ^2 referring to the highest filled orbital (frontier orbital) of the aromatic compound.

Nitration of Polycyclic Aromatic Hydrocarbons.—The success with which the present theory accounts for relative rates of electrophilic substitution reactions may be judged from the recently determined data [2] for nitration of polycyclic aromatic hydrocarbons. Nitration is a suitable reaction because it has been shown that the formation of a charge-transfer complex is the rate-determining step, at least for hydrocarbons which are not too reactive. Suitable values of the parameters $g_e^{\ddagger}$ [equation (8)] and $y_e^{\ddagger}$ [equation (10)], characterizing the transition state and the electrophil in this reaction, were first determined by trial and error. The value of $y_e^{\ddagger}$ would be expected to be greater than y_j for the frontier orbital of benzene, *i.e.*, greater than unity, and $g_e^{\ddagger}$ to be less than unity. The values $y_e^{\ddagger} = 2$, $g_e^{\ddagger} = 0{\cdot}6_1$ were found to be appropriate (these may not be the optimum values but $y_e^{\ddagger}$ is probably within $\pm 0{\cdot}5$ and g_e within $\pm 0{\cdot}1$ of the optimum values). Values of Z^0 calculated by using these values and equation (13), for the hydrocarbons studied by Dewar, Warford, and Mole,[2] and including charge-transfer from the frontier orbitals only, are listed in Table 1. To examine the effect of including charge transfer from the next-to-frontier orbitals equation (12) was solved and the resultant values are also listed in Table 1. It will be seen that the inclusion of the second occupied orbitals in the calculation scarcely affects the Z value in most cases. The extent to which the Z-values, calculated with two occupied orbitals included, correlate with experimental reaction rate constants is shown in Fig. 1. The success of this correlation provides support for the assumptions made in setting up the present theory (*e.g.*, the assumption that $X^{\ddagger}$ is independent of the nature of ArH); assumptions of this general type have of course been made in previous molecular-orbital theories of chemical reactivity.

The success of the correlation also implies that variations in rates of nitration can be ascribed primarily to variations in $\Delta E^{\ddagger}$, $\Delta S^{\ddagger}$ remaining constant or varying in proportion to variations in $\Delta E^{\ddagger}$.

Previously molecular-orbital treatments of electrophilic substitution have been based on calculations of π-electron densities, atom-localization energies or superdelocalizabilities; [3,4] for alternant hydrocarbons only the last two vary from one position to another. For comparison with Z-numbers the superdelocalizabilities have been computed for the positions studied experimentally; first-order approximations to atom-localization energies (the " reactivity-numbers " of Dewar) are already available.[2] The numerical values are given in Table 1 and the extent to which they correlate with the observed rates may be judged from Figs. 2 and 3. It is evident that Z-numbers show a better linear correlation with the logarithms of rates than do other theoretical quantities. With the exception of the points for triphenylene which lie well off the lines in all correlations and for which we can offer no theoretical explanation, all rates may be predicted from Z-values to better than a factor of 2 although the total range is more than $1 : 10^5$.

Dewar, Mole, and Warford have attributed most of the scatter of the points on Fig. 2 to steric effects. If the rate-determining step is the formation of a charge-transfer complex

[2] Dewar, Mole, and Warford, *J.*, 1956, 3581.
[3] Fukui, Yonezawa, and Nagata, *Bull. Chem. Soc. Japan*, 1954, **27**, 423.
[4] Fukui, Yonezawa, and Nagata, *J. Chem. Phys.*, 1957, **27**, 1247.

of the geometry envisaged in Part I, with the electrophil situated above the attacked carbon atom (aromatic plane horizontal) and the C–H bond scarcely stretched then the steric hindrance even at positions like the 4-position in phenanthrene would not be very great. It would be only when an adjacent carbon atom had a bulky substituent attached, or when a large electrophil was involved, that significant steric effects would be expected. However most of the small scatter of points in Fig. 1 could be attributed to small steric effects, although other factors, not primarily connected with π-electrons, such as variation in $\Delta S^{\ddagger}$ owing to differing extents of " solvent-freezing," etc., could equally be responsible.

FIG. 1. *Z-Values plotted as a function of rates of nitration of polycyclic hydrocarbons.*

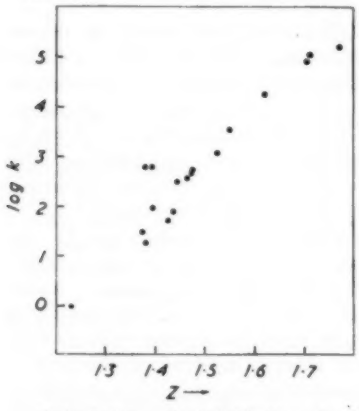
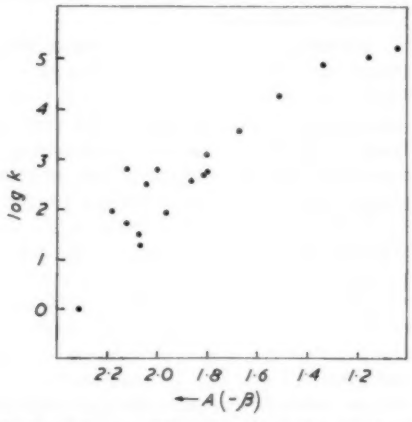


FIG. 2. *Atom-localization energies as a function of rates of nitration.*



Orientation of Substitution in Conjugated Hydrocarbons.—The Z-values for various positions in a conjugated hydrocarbon are determined primarily by Y_f and c_f^2, the lower filled orbitals making little contribution except when one of them is nearly degenerate with the frontier orbital. Thus the relative reactivities of different positions in a conjugated system are indicated by the values of c_f^2, *i.e.*, by the frontier electron density.[3] This explains the success of the frontier electron density method of accounting for orientation of substitution, and why frontier electron densities nevertheless do not indicate the relative reactivities of two positions in ***different*** conjugated systems. Such an explanation of the significance of frontier electron densities had previously been lacking. Fukui *et al.*[3] have suggested that reactivities should be characterized by superdelocalizabilities and the frontier electron densities make a major contribution to these but the proportional contributions from other occupied orbitals to superdelocalizabilities are considerably greater than to Z-values.

It has already been shown [5] that frontier electron densities satisfactorily account for the orientation of substituents in alternant hydrocarbons; Z values will likewise be in agreement with observed orientations for such compounds. To demonstrate further the agreement between orientations predicted by Z-values and observed orientations, the positions of highest Z-value for some non-benzenoid hydrocarbons and the observed orientations are given in Table 2. Charge transfer from the two highest-energy occupied orbitals of the hydrocarbons was included and parameters appropriate for nitration were used. The position preferentially attacked by electrophils is known in all cases except that of pleiadiene. In each case the position attacked is that of highest Z-value. The case of fluoranthene is of interest because the calculated π-electron densities [6] are greater

[5] Fukui, Yonezawa, and Shinger, *J. Chem. Phys.*, 1952, **20**, 722.
[6] " Dictionary of Values of Molecular Constants," edited by C. A. Coulson and R. Daudel, Centre national de la Recherche scientifique, Paris, 1955, Vol. III, Part I, p. 14.

than unity at the 2- and the 8-position, less than unity at the 1- and the 3-position yet, as correctly predicted by Z-values, it is the 3-position which is preferentially nitrated.[7]

Although pleiadiene has been nitrated[8] the position of attack has not yet been

TABLE 1.

Compound	Posn.	log k *	Z (*a*)	Z (*b*)	A †	S ‡	T §
Benzene		0	1·207	1·223	2·31	0·833	0·75
Diphenyl	2	1·48	1·345	1·373	2·07	0·910	0·960
	4	1·26	1·381	1·381	2·07	0·894	0·929
Naphthalene	1	2·67	1·474	1·474	1·81	0·994	0·929
	2	1·70	1·419	1·427	2·12	0·873	0·973
Phenanthrene	1	2·56	1·455	1·465	1·86	0·977	0·955
	2	1·96	1·396	1·397	2·18	0·860	0·999
	3	2·48	1·447	1·447	2·04	0·893	0·962
	4	1·90	1·424	1·437	1·96	0·939	0·979
	9	2·69	1·482	1·483	1·80	0·997	0·934
Pyrene	1	4·23	1·618	1·620	1·51	1·115	0·958
Triphenylene	1	2·78	1·377	1·393	2·00	0·888	0·952
	2	2·78	1·377	1·381	2·12	0·928	0·952
Chrysene	2	3·54	1·552	1·552	1·67	1·044	0·949
Perylene	3	4·89	1·700	1·705	1·34	1·195	0·970
Benzopyrene	6	5·03	1·712	1·712	1·15	1·408	0·947
Coronene		3·06	1·517	1·525	1·80	0·991	0·960
Anthanthrene	6	5·19	1·769	1·771	1·03	1·504	0·964

(*a*) Considering charge transfer from frontier orbital only. (*b*) Including frontier and next highest filled orbital.

* Relative rates of nitration (see ref. 10).

† Atom localization energies estimated by first order perturbation theory (see ref. 10).

‡ Superdelocalizabilities (see ref. 4).

§ Extent of charge transfer in the transition state [see equation (19)].

TABLE 2.

Hydrocarbon	Posn.	Z	Most active posn.	Hydrocarbon	Posn.	Z	Most active posn.
Azulene (I)	1	1·663	1	Fluoranthene (IV)	3	1·454	3
Acenaphthylene (II)	1	1·505	1	Diphenylene (V)	2	1·598	2
Pleiadiene (III)	3	1·821	?				

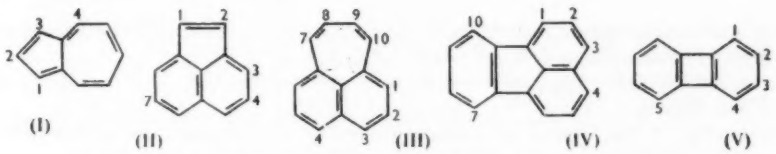


TABLE 3. *Z-Values for pleiadiene, all occupied orbitals included.*

Posn.	Z	Posn.	Z
1	1·824	7	1·808
2	1·763	8	1·792
3	1·832		

established. From calculated Z-values it is predicted to be the 3-position (contrast π-electron density data[9] which show the 1-position to have the highest reactivity) and the magnitude of Z indicates extraordinarily high reactivity.* In such circumstances the nitronium ion might be expected to show little discrimination between the various positions of the hydrocarbon. To examine this point theoretically the Z-values of all positions were computed, including *all* occupied orbitals in the calculation because even small

* For compounds of such high reactivity the formation of the charge-transfer complex may no longer be rate-determining (see Part I).

[7] von Braun and Manz, *Annalen*, 1931, **488**, 111; 1932, **496**, 170.

[8] Boekelheide and Vick, *J. Amer. Chem. Soc.*, 1956, **78**, 653.

[9] Pullman, Pullman, Berthier, and Pontis, *J. Chim. phys.*, 1952, **49**, 20.

contributions from lower orbitals might alter the order of Z-values. The results are given in Table 3. It seems likely that both the 1- and the 3-nitro-derivatives would be formed in appreciable amounts judging from the Z-values.

Electrophilic Substitution in Benzene Derivatives: Inductive Effect only.—As a further test of the proposed molecular-orbital treatment of chemical reactivity let us consider the inductive effect of substituents on the Z-numbers for benzene. In the molecular-orbital theory the inductive effect amounts to a perturbation to the Coulomb integral of the carbon atom to which the substituent is attached. Let the change in the Coulomb integral be $h\beta$. This perturbation splits the degeneracy of the frontier orbitals of benzene, the energy of only one orbital being changed to the first order in h. The perturbations to the orbital

FIG. 3. *Superdelocalizabilities as a function of rates of nitration.*

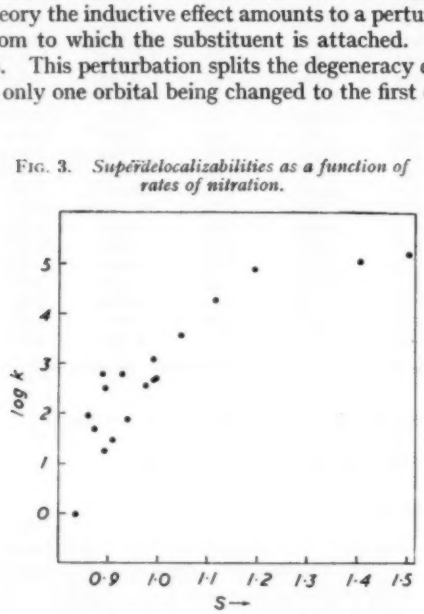
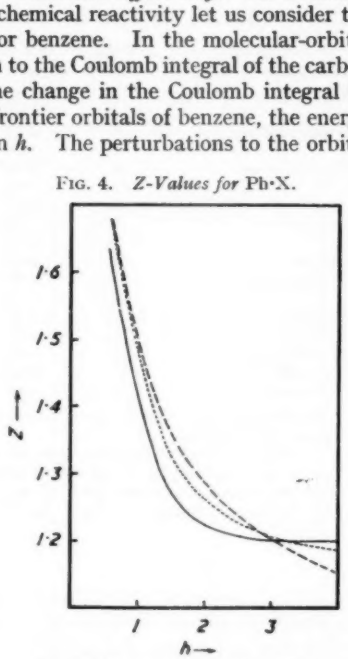


FIG. 4. *Z-Values for* Ph·X.



. . . *ortho*, —— *meta*, – – – *para*.
$k = 0{\cdot}8$, $h^{(1)} = 0{\cdot}1h$.

energies and coefficients are conveniently obtained by the method of Bassett and Brown:[10]

Unperturbed orbital: $y_f = 1$, $c_o^2 = 1/4$, $c_m^2 = 1/4$, $c_p^2 = 0$.

Perturbed orbital: $y_{f-1} = 1 + h/3$, $c_o^2 = 1/12 - 11h/108$; $c_m^2 = 1/12 + 7h/108$; $c_p^2 = 1/3 + 4h/108$.

The change in the Z-value for benzene caused by this perturbation may be derived by a first-order perturbation treatment of equation (12). It is:

$$\delta Z = 2g_e^{\pm 2} \sum_j \frac{c_j^2 \delta Y_j + (Z_b - Y_j)\delta c_j^2}{(Z_b - Y_j)^2} \left\{ 1 + 2g_e^{\pm 2} \sum_k \frac{c_k^2}{(Z_b - Y_k)^2} \right\}^{-1} \quad . \quad . \quad (15)$$

where Z_b is the Z-value of unperturbed benzene and the summations are over all occupied orbitals, or over those orbitals from which charge transfer is considered. If we consider only the frontier orbitals of benzene and use the values of parameters found appropriate for nitration at 0° (see above) as typical values, then $Z_b = 1{\cdot}207$ and we find:

Position	*ortho*	*meta*	*para*
δZ	$-0{\cdot}125h$	$-0{\cdot}037h$	$-0{\cdot}265h$

These values are in harmony with the accepted properties of inductively substituted benzenes. For $-I$ substituents (h positive) the Z-values require *meta*-substitution with deactivation (Z less than Z_b). For $+I$ substituents (*e.g.*, alkylbenzenes) the Z-values require *ortho–para*-substitution with activation.

[10] Bassett and R. D. Brown, *Proc. Phys. Soc.*, 1958, *A*, **71**, 724.

The results for positive h also are appropriate for pyridine in which *meta*-substitution with deactivation occurs.

It has often been assumed that inductive effects fall off along a chain of atoms in geometric progression.[11] To allow for this in the molecular-orbital treatment auxiliary inductive parameters $h^{(1)}$, $h^{(2)}$, ... are included such that for an atom separated from the centre of perturbation by $n - 1$ atoms, the Coulomb integral is increased by $h^{(n)}\beta$ with $h^{(n)} = \theta^n h$, θ being a number such that $0 < \theta < 1$. Properties of aliphatic compounds suggest the value [11] $\theta = \frac{1}{3}$. Although until recently there was no strong evidence from the *chemical reactivities* of conjugated systems that it was necessary to include such auxiliary parameters, SCF[12] and SCE [13,14] calculations show that parameters of this type should be included in the simple MO calculations. However the origin of these auxiliary inductive effects may be traced to penetration integral effects so that they are not directly comparable to the inductive effects observed in saturated compounds and the value $\theta = \frac{1}{3}$ is therefore not necessarily the appropriate one (it is not certain yet that the geometric progression formula is apposite). The perturbation calculations have therefore been performed by using general values of $h^{(n)}$. The relevant orbital data are:

$$\delta y_f = (1/2)h^{(1)} + (1/2)h^{(2)};\ \delta y_{f-1} = (1/3)h^{(0)} + (1/6)h^{(1)} + (1/6)h^{(2)} + (1/3)h^{(3)}$$

Position	δc_f^2	δc_{f-1}^2
ortho	$(1/8)h^{(1)} - (1/8)h^{(2)}$	$(1/216)(-22h^{(0)} - 5h^{(1)} + 13h^{(2)} + 14h^{(3)})$
meta	$-(1/8)h^{(1)} + (1/8)h^{(2)}$	$(1/216)(14h^{(0)} + 13h^{(1)} - 5h^{(2)} - 22h^{(3)})$
para	0	$(1/216)(8h^{(0)} + 28h^{(1)} - 44h^{(2)} + 8h^{(3)})$

and, for the values of parameters appropriate for the nitration reaction

Position	δZ
ortho	$-[0{\cdot}125h^{(0)} + 0{\cdot}302h^{(1)} + 0{\cdot}390h^{(2)} + 0{\cdot}037h^{(3)}]$
meta	$-[0{\cdot}037h^{(0)} + 0{\cdot}390h^{(1)} + 0{\cdot}302h^{(2)} + 0{\cdot}125h^{(3)}]$
para	$-[0{\cdot}265h^{(0)} + 0{\cdot}074h^{(1)} + 0{\cdot}250h^{(2)} + 0{\cdot}265h^{(3)}]$

To determine the effect of including charge transfer from the remaining occupied orbital of benzene also, the perturbation calculations were repeated with this extension. The relevant data for the lowest filled orbital are:

$$\delta y_{f-2} = (1/6)h^{(0)} + (1/3)h^{(1)} + (1/3)h^{(2)} + (1/6)h^{(3)}$$

Position	δc_{f-2}^2
ortho	$(1/216)[5h^{(0)} + 22h^{(1)} - 14h^{(2)} - 13h^{(3)}]$
meta	$(1/216)[-13h^{(0)} - 14h^{(1)} + 22h^{(2)} + 5h^{(3)}]$
para	$(1/216)[-19h^{(0)} - 26h^{(1)} + 10h^{(2)} + 35h^{(3)}]$

With the values of parameters appropriate for nitration (Z_b now is 1·223) we find

	δZ
ortho	$-[0{\cdot}125h^{(0)} + 0{\cdot}282h^{(1)} + 0{\cdot}390h^{(2)} + 0{\cdot}041h^{(3)}]$
meta	$-[0{\cdot}041h^{(0)} + 0{\cdot}390h^{(1)} + 0{\cdot}282h^{(2)} + 0{\cdot}125h^{(3)}]$
para	$-[0{\cdot}265h^{(0)} + 0{\cdot}083h^{(1)} + 0{\cdot}249h^{(2)} + 0{\cdot}240h^{(3)}]$

As was found when considering the nitration of polycyclic hydrocarbons the inclusion of the lower orbital in the calculations has only a small effect on the calculated Z-values.

Selectivity of Electrophils.—The concept of selectivity of electrophils—that the more reactive the electrophil the less discriminating it is in selecting the site of substitution—was put on a quantitative footing by H. C. Brown and Nelson [15] who considered partial rate factors for substitution in toluene. Calling the common logarithm of the ratio of partial rate factors for the *para* and a *meta* position the selectivity factor F_s, they found

$$\log p_f = AF_s \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

[11] Dewar, *J.*, 1949, **463**.
[12] R. D. Brown and Heffernan, *Austral. J. Chem.*, 1957, **10**, 211.
[13] R. D. Brown and Heffernan, *Trans. Faraday Soc.*, 1958, **54**, 757.
[14] R. D. Brown and Heffernan, results in course of publication.
[15] H. C. Brown and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 6292.

the constant A being independent of the electrophil and having the value 1·3. The present molecular-orbital treatment provides a quantitative theoretical basis for this relationship. In terms of Z-values we have

$$\log p_f = -\frac{\beta}{2{\cdot}303RT}(Z_p - Z_b)$$

and

$$F_s = -\frac{\beta}{2{\cdot}303RT}(Z_p - Z_m)$$

Thus the constant A in (16) becomes

$$A = (Z_p - Z_b)/(Z_p - Z_m).$$

It now has to be shown that A is independent of the nature of the electrophil in the case of an inductively substituted benzene such as toluene. For such benzene derivatives the perturbation treatment given above may be used. For benzene the expression in braces in (15) has the same value for all positions and so

$$A = \sum_j \frac{c_{jp}^2\delta Y_j + (Z_b - Y_j)\delta c_{jp}^2}{(Z_b - Y_j)^2}\left\{\sum_k \frac{(c_{kp}^2 - c_{km}^2)\delta Y_k + (Z_b - Y_k)(\delta c_{kp}^2 - \delta c_{km}^2)}{(Z_b - Y_k)^2}\right\}^{-1} \quad (17)$$

It has been seen that the inclusion of the lowest occupied orbital in the calculation has little effect; if it is omitted then (17) can be simplified, remembering that $Y_f = Y_{f-1}$:

$$A = \frac{\frac{1}{3}\delta Y_{f-1} + (Z_b - Y_f)\delta c_{f-1,p}^2}{\frac{1}{4}\delta Y_{f-1} - \frac{1}{4}\delta Y_f + (Z_b - Y_f)(\delta c_{f-1,p}^2 - \delta c_{f,m}^2 - \delta c_{f-1,m}^2)}$$

If we include only the primary inductive parameter $h^{(0)}$, and use equation (14) to estimate $Z_b - Y_f = 2g_e^{\ddagger 2}/3Y_f$, we find:

$$A = \frac{36 - 8g_e^{\ddagger 2}/Y_f}{27 + 6g_e^{\ddagger 2}/Y_f} \quad \ldots\ldots\ldots \quad (18)$$

For small values of $g_e^{\ddagger 2}/Y_f$, A is independent of the nature of the electrophil, its value being 1·3 which is fortuitously in excellent agreement with the experimental value. For nitration $g_e^{\ddagger 2}/Y_f = 0{\cdot}75$ and the value of this ratio would not be expected to vary greatly from this value, especially as both $g_e^{\ddagger}$ and Y_f would be expected to increase with increasing reactivity of the electrophil. If the nitration values are used, then instead of the use of the approximate expression (18) A can be calculated directly from the perturbation theory results: $A = 0{\cdot}265/(0{\cdot}265 - 0{\cdot}041) = 1{\cdot}2$ when charge transfer from all orbitals is included and only the primary inductive parameter $h^{(0)}$ is used. The value is altered only slightly when auxiliary inductive parameters are included.

Thus on the assumption that the ratio $g_e^{\ddagger}/Y_f$ for benzene does not vary too greatly with the nature of the electrophil, the present theory accounts for H. C. Brown and Nelson's observations on selectivity relationships for electrophils and requires only the use of perturbation theory.

The present treatment of the selectivity factors implies that the value of A should be independent of the nature of the *substrate* provided that this is an inductively substituted benzene. This conclusion is borne out by published diagrams [16] of log p_f *versus* F_s for various substrates. Those with purely inductive substituents have gradients indistinguishable from that for toluene although substrates with conjugating substituents show large variations in gradient.

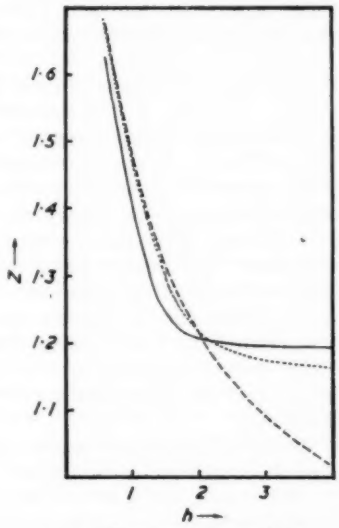
Benzene Substituents with both Mesomeric and Inductive Effects.—To examine the ability of the present theory to account for electrophilic substitution in substituted benzenes in which the substituent exerts both a mesomeric and an inductive effect, calculations of Z-values have been performed for the conjugated system (VI), X being characterized by a

[16] Nelson, *J. Org. Chem.*, 1956, **21**, 145.

Coulomb integral $h\beta$ relative to carbon, by a resonance integral $\beta_{cx} = k\beta$, and by an inductive Coulomb integral $h^{(1)}\beta$ for the carbon atom to which X is attached. Representative calculations for values of h, k, and $h^{(1)}$ which are likely to be appropriate for substituents such as halogen, OH, or NH_2, are summarized in Figs. 4, 5, and 6.

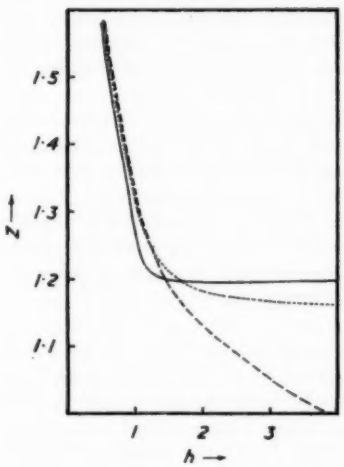
The results are in agreement with the main features of substitutions observed in this kind of benzene derivative—*ortho-para*-substitution with the overall level of reactivity of the molecule decreasing as the electronegativity of the substituent increases. The relative separations of the curves for the three positions are seen to depend particularly on the magnitude of the auxiliary inductive parameter (and this would be influenced by inclusion of further inductive parameters as in the geometric-progression formula mentioned above), and to some extent on the degree of conjugation of the substituent with the ring (*i.e.*, or the value of k). In due course it is intended to study more fully the variation of Z-values

FIG. 5. *Z-Values for* Ph·X.



. . . *ortho*, — *meta*, – – – *para*.
$k = 0{\cdot}8$, $h^{(1)} = 0{\cdot}25h$.

FIG. 6. *Z-Values for* Ph·X.



. . . *ortho*, —— *meta*, – – – *para*.
$k = 0{\cdot}5$, $h^{(1)} = 0{\cdot}25h$.

with the values of the molecular-orbital parameters of the substituent to attempt to account in more detail for observed variations in rates of nitration of benzene derivatives.

Extent of Charge Transfer.—In Part I the approximate formula $T = 1 - (H_{01}^{\ddagger}/\Delta^{\ddagger})^2$ was derived for the extent of charge transfer in the transition state for formation of the initial complex. If equations (7) and (11) are substituted in this expression we have

$$T \approx 1 - 2g_e^{\ddagger 2}c_f^2/Y_f^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (19)$$

Values of T derived from (19) are given in Table 1. In all cases except that of benzene, charge transfer is substantially complete, indicating that the formula (VII) used in Part I to represent charge-transfer complexes is an acceptable one, at least in the case of the complexes which intervene in the nitration of aromatic hydrocarbons.

The Significance of Other Molecular-orbital Quantities.—The significance of frontier electron densities in the light of the present mechanism of electrophilic substitution has been discussed above; they are expected to indicate the relative Z-values of different positions in the same molecule. Superdelocalizabilities were introduced as an approximate

estimate of the variation in activation energy for the substitution reaction, the sp^3 configuration being assumed for the transition state. Although there is strong evidence that (VIII) is not the rate-determining transition state in nitration and bromination reactions but rather an unsymmetrical configuration somewhat like (VII) [see Part I], the theoretical treatment leading to the superdelocalizability concept could equally be applied to structures like (VII). Thus superdelocalizabilities are an alternative criterion of reactivity

(VI)

(VII)

(VIII)

according to the present mechanism. We believe that they are less satisfactory than Z-values because of difficulties relating to the electronegativity of E and the extent of charge transfer. These difficulties were noticed by Fukui *et al.*,[4] but they were not able to devise a means of circumventing them for numerical work. The difficulties are avoided by the present configuration-interaction technique.

Previous treatments based on the transition state (VIII) coupled reactivity of a position with its π-electron density or its atom-localization energy, according to two alternative approximate views of the structure of (VIII).[17] This procedure has the disadvantage that the prediction of orientation in alternant hydrocarbons was based on localization energies, because all positions have the same π-electron density, yet when the orientations predicted by charge densities differ from those predicted by localization energies (as often happens for heterocyclic molecules) the experimental orientation almost always agrees with that predicted by π-electron densities, not by localization energies.* The present treatment is based on a single theoretical quantity—the Z number—and so this dilemma does not arise. It has the further advantage that the nature of the electrophil, and the possibility that different electrophils may yield differing relative reactivities for a series of aromatic compounds, are explicitly recognized in the theory. This more comprehensive viewpoint is achieved at the cost of introducing two parameters, $y_e^{\ddagger}$ and $g_e^{\ddagger}$, characteristic of the electrophil, which for the present must be evaluated empirically.

By using valence-bond terminology the present approach may be compared more pictorially with the π-electron density and delocalization energy methods. When the π-electron density is used as a criterion of reactivity this is equivalent to viewing the structure of the transition state as $E^+ \ldots ArH$, the bonding between the reactants being purely ionic. When localization energies are used it amounts to assuming the structure of the transition state to be $E{-}ArH^+$ with a pure covalent bond between the electrophil and the carbon atom undergoing substitution, the bond being strong enough to eliminate this carbon from the conjugated system. In the present charge-transfer configuration approach the structure of the transition state is regarded as predominantly corresponding to Ψ_1 with small contributions from Ψ_0 and other configurations. Now Ψ_1 is readily decomposed into

$$\sum_{\mu} c_{f\mu}\{\mathscr{A}[\psi_1(1)\alpha(1)\ldots\chi_\mu(n-1)\alpha(n-1)\chi_e(n)\beta(n)] + \mathscr{A}[\psi_1(1)\alpha(1)\ldots\chi_e(n-1)\alpha(n-1)\chi_\mu(n)\beta(n)]\}/\sqrt{2},$$

i.e., into a sum of configurations in which the electron transferred to the electrophil orbital is paired with the frontier-orbital electron, located in turn in each $2p\pi$-orbital of the conjugated system of ArH. Thus the transition state is viewed as predominantly a " resonance hybrid " of $E{-}ArH^+$ structures in which the bond links the electrophil in

* Orientations in unreactive species such as protonated cations of heterocycles follow localization energies however.[18]

[17] R. D. Brown, *Quart. Rev.*, 1952, **6**, 63.
[18] R. D. Brown, " Current Trends in Heterocyclic Chemistry," Butterworths, London, 1958, p. 13.

turn to each carbon atom of the aromatic system, the bonds between the electrophil and every carbon atom except the μth being very long and energetically negligible; the relative weights of the structures are given by the frontier electron densities. A small contribution from Ψ^*_0, corresponding to $E^+ \ldots ArH$, and from other configurations which may be dissected as above, are also implied in the complete eigenfunction. In the charge-transfer approach the bond between the electrophil and the μth carbon atom is not strong enough to exclude the carbon atom from the conjugated system of the aromatic system although the extent of conjugation within the aromatic system (represented, say, by the sum of the bond orders) is reduced in the charge-transfer complex as compared with the original aromatic compound.

It has not been possible to demonstrate theoretically any analytical relationship between Z-numbers and π-electron densities, or between Z-numbers and localization energies. However qualitatively it seems reasonable that these quantities will be roughly related because presumably the transfer of charge from an aromatic compound to an electrophil would be easiest (energetically) from the position of highest charge in the aromatic system; and the original " isolated molecule " viewpoint [17] justifying the correlation of π-electron densities and chemical reactivity is equally applicable to the present mechanism of substitution. The Wheland localization-energy approach amounts to giving extreme importance to just one of the configurations which enter into the charge-transfer theory.

Distinction between π- and σ-Electrons.—The charge-transfer complexes are not planar molecules and so the symmetry distinction between π- and σ-electrons is lost. However the more important distinction between π- and σ-electrons is that the former are more loosely bound to the molecule then the latter, and the success of the " π-electron approximation," widely adopted in theoretical chemistry, in which detailed interactions and motions are considered for π-electrons only, the σ-electrons being treated as part of the core, seems to depend largely on the energy difference between σ- and π-electrons although the strict orthogonality between π- and σ-orbitals has certain useful consequences for establishing a partial variational theorem.[19]

If the energies of the π-electrons in ArH are not too greatly reduced when the charge-transfer complex is formed then there will be in the complex two groups of electrons of energies similar to the π- and σ-electrons in ArH and it seems convenient still to designate them as π- and σ-electrons for easy reference.*

In the charge-transfer complexes the bond between the electrophil and the aromatic compound is a " resonance hybrid " of a series of bonds involving each conjugated atom in ArH, all but one of these bonds being extremely weak, the strongest of them being about $0{\cdot}6\beta$ (in the case of nitration complexes) and this having a weight in the " resonance hybrid " typically around 0·1 to 0·4. Thus the interaction is weak enough for the energy distinction between π- and σ-electrons still to apply.

However it may happen in some cases, possibly with " addition " reagents which have orbitals that appreciably overlap more than one of the aromatic compound and give addition reactions, that stronger interactions are involved, appreciably lowering the energies of the most loosely bound electrons so that their distinction from the σ-electrons is not so marked. It is hoped to take up this aspect further in a subsequent publication on addition reactions.

The author is grateful to Professor B. Pullman of the University of Paris for communicating eigenvectors and eigenvalues of anthanthrene, from which the reported Z-values of this molecule were computed, and to Mr. R. D. Harcourt who obtained eigenvectors and eigenvalues on the electronic computer CSIRAC from which the data in Figs. 4—6 were computed.

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VICTORIA, AUSTRALIA. [*Received, August 18th*, 1958.]

* This represents a further generalization of the π–σ terminology, just as the currently accepted terminology is an extension of the original one applying to linear molecules only.

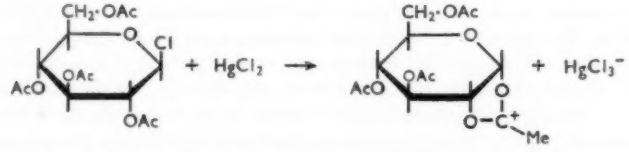
[19] Lykos and Parr, *J. Chem. Phys.*, 1956, **24**, 1166.

443. *The Reactivity of the* O-*Acylglycosyl Halides. Part VII.* Anomerisation of Tetra-*O-*acetyl-*β*-*D*-glucosyl Chloride.*

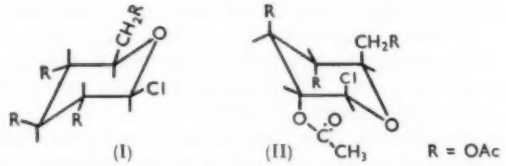
By G. L. Mattok and G. O. Phillips.

The anomerisation of tetra-*O*-acetyl-β-D-glucosyl chloride in acetone, measured polarimetrically, is a first-order reaction. The reaction rate is enhanced by addition of lithium chloride or bromide, and by increasing the ionising power of the medium. Experiments using lithium radio-bromide establish that there is negligible halogen-exchange, and that anomerisation is the main process. The results cannot be accounted for solely on the basis of complete ionisation of the halide, and an intramolecular mechanism is therefore postulated for the anomerisation.

Solvolytic reactions of tetra-*O*-acetyl-β-D-glucosyl chloride proceed by way of an intermediate cyclic carbonium ion arising from the participation of the neighbouring group at position 2. Addition of mercuric chloride or other electrophilic catalysts increases the reaction rate by assisting the removal of the halogen without affecting the general nature of the ionisation process:



Decreasing the ionising power of the medium markedly decreases the rate of solvolysis.[1] However, in dry acetone, and in other solvents of low ionising power which do not react with the halogen atom, tetra-*O*-acetyl-β-D-glucosyl chloride spontaneously rearranges to the anomeric form.[2] Hassel and Ottar [3] considered this reaction to be related to the general substitution reaction of the S_N2 type where the new and the old substituent were identical. On this basis they considered that interaction between *cis*-erected (axial) 1- and 5-substituents on the same side of the ring is the main factor governing the stability



of the anomeric *O*-acylglycosyl halides. Lemieux,[4] however, regards this as an oversimplification and considers that the theory is inconsistent with spontaneous anomerisation. For example, according to Hassel and Ottar's theory, tetra-*O*-acetyl-β-D-glucosyl chloride would exist in the C1 conformation (I) since the 1C conformation (II) would be highly unstable. However, participation of the 2-acetoxy-group in replacement reactions at position 1, now well established, requires the molecule to assume the 1C conformation at the first stage of the reaction. In the present work, the mechanism of anomerisation is investigated, and the rôle of lithium halides clarified.

* Part VI, *J.*, 1958, 130.

[1] Mattok and Phillips, *J.*, 1957, 268.
[2] Schlubach, Stadler, and Wolf, *Ber.*, 1928, **61**, 287.
[3] Hassel and Ottar, *Acta Chem. Scand.*, 1947, **1**, 929.
[4] Lemieux, *Adv. Carbohydrate Chem.*, 1954, **9**, 1.

Results

Order of the Reaction.—The rate of anomerisation of tetra-*O*-acetyl-β-D-glucosyl chloride is of the first order; good first-order constants, calculated from the first-order rate equation, are given throughout the run (Table 1). Varying the initial concentration of the sugar halides within a two-fold range does not influence the rate constant (Table 2).

Addition of Lithium Halides.—The rate of anomerisation is enhanced on addition of lithium halides. The first-order constant increases linearly with lithium bromide concentration in the

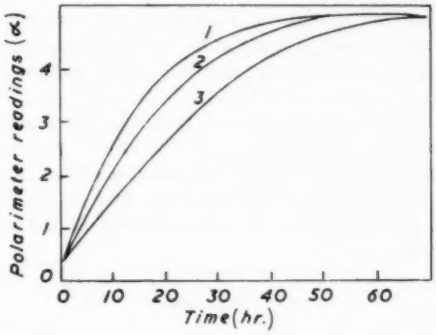
TABLE 1. *Anomerisation of tetra-O-acetyl-β-D-glucosyl chloride in acetone at 25°. First-order constants.*

Time (min.)	4	29	55	84	130	186
α	−0·02°	+0·04°	+0·11°	+0·19°	+0·30°	+0·45°
10^6k_1 (sec.$^{-1}$)		9·95	9·85	9·99	9·65	9·85

TABLE 2. *First-order anomerisation of tetra-O-acetyl-β-D-glucosyl chloride. Variation of initial concentrations.*

10^2[RCl] (M)	7·92	6·45	4·98	4·11	3·6
10^6k_1 (sec.$^{-1}$)	9·90	9·72	9·63	9·81	9·69

range 1·9—5·0 × 10^{-2}M and for lithium chloride in the range 5·0—7·4 × 10^{-2}M (Table 3). The order with respect to lithium chloride is 0·5, and with respect to lithium bromide is 0·4. Extrapolation of the rate constants indicates that the linear relation is maintained to zero concentration of lithium halide. The extrapolated value of k_1 for zero concentration of lithium



Anomerisation of tetra-O-acetyl-β-D-glucosyl chloride in acetone with or without lithium bromide or chloride.

[RCl] = 0·05M. 1, [LiBr] = 0·05M. 2, [LiCl] = 0·05M. 3, *Dry acetone.*

chloride is 9·3 × 10^{-6} sec.$^{-1}$ and for that of lithium bromide is 9·2 × 10^{-6} sec.$^{-1}$; and these values are in good agreement with the rate of anomerisation in dry acetone (k_1 9·5 × 10^{-6} sec.$^{-1}$). The final rotation of the solution is not affected by the presence of either of the lithium salts see (Figure). The constant value corresponds to 80% conversion of the β- into the α-anomer.

TABLE 3. *Effect of lithium halides in the anomerisation of tetra-O-acetyl-β-D-glucosyl chloride in acetone at 25°. First-order constants.*

[LiBr] (10^{-2}M)	5·01	4·57	4·16	5·37	2·52	1·87	[LiCl] (10^{-2}M)	7·43	6·33	5·00
10^5k_1 (sec.$^{-1}$)	1·81	1·78	1·66	1·52	1·38	1·24	10^5k_1 (sec.$^{-1}$)	1·83	1·75	1·52

Rate of Exchange with Lithium Radio-bromide.—Lithium radio-bromide was added to tetra-*O*-acetyl-β-D-glucosyl chloride in acetone at 25°, and the sugar halide examined for radioactivity at intervals, after separation from the inorganic halide. The proportion of radioactivity transferred to the sugar halide in 0·5, 2·5, and 6 hr. was 0·0, 0·05, and 0·5% respectively.

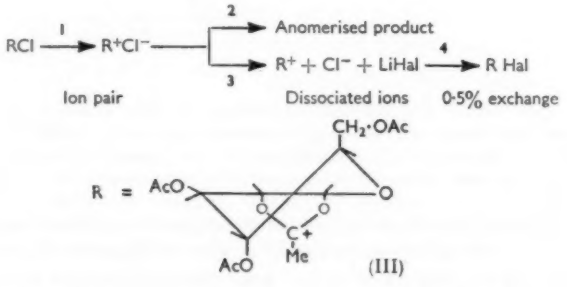
Effect of Varying the Ionising Power of the Solvent.—In benzene (ε 2·28 at 20°) no anomerisation was detected after 48 hr. In nitromethane (ε 39·4 at 20°) first-order anomerisation occurred with k_1 1·45 × 10^{-5} sec.$^{-1}$ at 25°, which is a 50% increase on the anomerisation rate in dry acetone (ε 21·0 at 20°).

Discussion

Our results support an ionic mechanism for the anomerisation of tetra-*O*-acetyl-β-D-glucosyl 1-chloride rather than the bimolecular replacement suggested by Hassel and Ottar.[3] In dry acetone the rate is dependent on the first power of the concentration of sugar halide only, and on the ionising power of the solvent. Addition of lithium halides slightly increases the rate. The results indicate that the halide ions from the lithium salts do not participate by a bimolecular process, but exert a positive salt effect which facilitates the partial ionisation; this is supported first by experiments with lithium radio-bromide wherein no appreciable radioactivity was transferred to the sugar halide; and secondly, for tetra-*O*-acetyl-β-D-glucosyl chloride in acetone, the final optical rotation of the solution is independent of the nature of the lithium halide, indicating that the main product is the same in the presence of either lithium chloride or bromide (see Figure). Under comparable conditions for several *O*-acylglycosyl 1-halides, however, bimolecular exchange of halogen predominates. For example, when sodium iodide is added to tetra-*O*-acetyl-α-D-glucosyl bromide in acetone, the corresponding iodide[5] is formed. Evidence for similar exchange reactions will be presented in a later paper.

On theoretical grounds also it would be expected that ionisation to form the well-established cyclic ion (III) would be energetically more favourable than the S_N2 transition state [3] where there would be appreciable steric hindrance between the departing groups and the erected groups at positions 3 and 5.

The small amount of halogen exchange in the tracer experiments also indicates that the sugar halide does not completely ionise to give a free cyclic carbonium ion. Clearly the free ion would combine with radio-bromide ions present in the solution. Rather the insignificant amount of halogen exchange indicates an intramolecular mechanism involving the departing halogen atom. Mechanisms of this type by way of undissociated ion pairs now appear well founded. Lemieux and his collaborators [6] have shown that a similar mechanism operates during the anomerisation of acetylated alkyl glucopyranosides. Moreover, Winstein and Schreiber [7] pointed out that the ion-pair phenomenon can in principle be present in all processes which involve neighbouring participation. Salt effects involving lithium perchlorate in S_N1 acetolysis have also been explained in this way.[8] The mechanism of anomerisation in the presence of lithium halides may therefore be represented:



(III)

Ionisation occurs initially to give an undissociated ion pair, the carbonium ion R^+ (III) assuming the half-chair form and thus facilitating the conformation change 1C to C1 which occurs during the formation of tetra-*O*-acetyl-α-D-glucosyl chloride from the β-anomer.

[5] Fischer and Fischer, *Ber.*, 1910, **43**, 2535.
[6] Lemieux and Brice, *Canad. J. Chem.*, 1956, **34**, 1006; Lemieux and Cipera, *ibid.*, p. 906; Lemieux and Shyluk, *ibid.*, 1955, **33**, 120.
[7] Winstein and Schreiber, *J. Amer. Chem. Soc.*, 1952, **74**, 2165.
[8] Fainberg and Winstein, *ibid.*, 1956, **78**, 2763, 2767, 2780; Fainberg, Robinson, and Winstein, *ibid.*, p. 2777; Winstein and Clippinger, *ibid.*, p. 2784.

The main process (reactions 1 and 2) is intramolecular, leading to tetra-*O*-acetyl-α-D-glucosyl chloride, while a small amount of dissociation of the ion pair (reaction 3) allows halogen exchange (0·5%) with lithium halides (reaction 4).

It should be emphasised also that anomerisation is most unlikely in polar solvents such as methanol, which react with the sugar halide, as reported previously.[4] The agreement between the polarimetric and the titrimetric rate constant [1] for solvolysis of tetra-*O*-acetyl-β-D-glucosyl chloride supports this view and it may be concluded accordingly that the products are formed as a result of initial racemisation to the carbonium ion.

Experimental

Acetone was purified as described in earlier papers. Nitromethane was dried over phosphoric oxide, and the fraction boiling at 101—102° collected.

Tetra-*O*-acetyl-β-D-glucosyl chloride was prepared as described in Part V of this series.

The polarimetric technique used was described in Part IV,[9] and rate constants were evaluated from the initial rates of the anomerisation. Rotations were measured in 2·2 dm. polarimeter tubes with sodium light.

Lithium Radio-bromide.—^{82}Br was obtained from A.E.R.E., Harwell, as ammonium bromide with an initial activity of 35 mc. Treatment with an equivalent quantity of aqueous lithium hydroxide gave lithium radio-bromide. Impurities were removed by several recrystallisations from acetone. The γ-radiation (1·3 Mev) given off by the ^{82}Br necessitates using the conventional shielding and remote-handling procedures. The pure lithium radio-bromide was diluted before use with inactive lithium bromide, and the total bromide content estimated by Volhard's method.

Radioactivity Measurements.—The reaction mixture was prepared by mixing the sugar halide and an aliquot part of the standardised lithium radio-bromide in acetone, and kept at 25°. At intervals 5 ml. samples were withdrawn, the reaction was stopped by cooling to 0°, and the mixture was extracted with chloroform and water. The organic halide was present in the

Table 4. *Anomerisation of tetra-O-acetyl-β-D-glucosyl chloride in acetone.* [RCl] = 0·0411M.

Time (min.)...	3	27	51	74	98	166	188	221	20 hr.	45 hr.	∞
α	−0·03°	0·07°	0·13°	0·18°	0·23°	0·38°	0·43°	0·49°	2·30°	3·62°	3·84°

$(d\alpha/dt)_{t=0} = 2·2 \times 10^{-3}$ degree min.$^{-1}$. $k_1 = 9·5 \times 10^{-4}$ sec.$^{-1}$.

Table 5. *Anomerisation of tetra-O-acetyl-β-D-glucosyl chloride in the presence of lithium bromide in acetone.* [RCl] = 0·05M. [LiBr] = 0·05M.

Time (min.)...	4	17	33	50	75	89	131	147	166	206	∞
α	−0·04°	0·06°	0·15°	0·24°	0·38°	0·44°	0·65°	0·72°	0·81°	1·00°	4·66°

$(d\alpha/dt)_{t=0} = 5·1 \times 10^{-3}$ degree min.$^{-1}$. $k_1 = 1·81 \times 10^{-3}$ sec.$^{-1}$.

Table 6. *Anomerisation of tetra-O-acetyl-β-D-glucosyl chloride in the presence of lithium chloride in acetone.* [RCl] = 0·05M. [LiCl] = 0·0743M.

Time (min.)...	10	19	49	63	78	91	116	193	336	365	∞
α	0·03°	0·10°	0·25°	0·35°	0·40°	0·45°	0·57°	0·92°	1·52°	1·65°	4·60°

$(d\alpha/dt)_{t=0} = 5·05 \times 10^{-3}$ degree min.$^{-1}$. $k_1 = 1·83 \times 10^{-3}$ sec.$^{-1}$.

Table 7. *Anomerisation of tetra-O-acetyl-β-D-glucosyl chloride in nitromethane.* [RCl] = 0·05M.

Time (min.)	5	14	30	56	77	106	147	185	∞
α	0·06°	0·09°	0·13°	0·22°	0·29°	0·40°	0·61°	0·82°	4·66°

$(d\alpha/dt)_{t=0} = 3·9 \times 10^{-3}$ degree min.$^{-1}$. $k_1 = 1·45 \times 10^{-3}$ sec.$^{-1}$.

former and the lithium halides in the latter. The radioactivity of the two extracts was measured in a standard liquid-type Geiger–Müller counter-tube. The efficiency of the extraction

[9] Mattok and Phillips, *J.*, 1956, 1836.

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was examined and by standardising the procedure a correction was applied to allow for incomplete extraction. A typical extraction-efficiency test is given here: At zero time a 5 ml. aliquot part of the reaction mixture was extracted with chloroform (8 ml.) and water (8 ml.). The chloroform layer in 5 min. gave 65 counts, while in the same counting time the water layer recorded 11,041 counts. The extraction efficiency is thus 99·4%. This small correction may therefore be applied to an identical extraction procedure, irrespective of the fall in radioactivity of the reaction mixture owing to the low half-life (36 hr.) of ^{82}Br. Accordingly the percentage exchange at successive time intervals may be obtained from the ratio of the radioactivity of the chloroform and the water extracts.

Tables 4—7 show typical runs, at 25°, only a part of the experimental observations being given.

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UNIVERSITY COLLEGE, CARDIFF. [*Received, November 28th,* 1958.]

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444. *Disaccharides from Fucoidin.*

By R. H. CÔTÉ.

A sample of fucoidin, a seaweed material made up of sulphated fucose, has been partially hydrolysed by acetolysis. Amongst the products liberated, three disaccharides have been isolated and characterised as 2-, 3-, and 4-*O*-α-L-fucopyranosyl-L-fucose. Comment is made concerning the structure of fucoidin in the light of these and earlier results.

FUCOIDIN, found in several types of seaweed, is commonly designated as a polyfucose ethereal sulphate. From methylation studies, Conchie and Percival suggested that 1 : 2-linked fucose units are the main linkages present but others also contribute to the fucoidin structure.[1] Indeed, after acetolysis of fucoidin and reduction, O'Neill was able to isolate and characterise by periodate oxidation a fucobi-itol containing a 1 : 2-linkage.[2] It was thought that such a polysaccharide would be a suitable source of different fucose-containing disaccharides, which were needed as reference compounds to assist in the identification of partial acid hydrolysis products from blood-group substances.[3]

After acetolysis of fucoidin, we have isolated three disaccharides A, B, and C. None of the corresponding fucobi-itols could be detected on chromatograms by the acidic benzidine spray [4] which quickly reveals non-reducing furanoside structures such as sucrose and methyl fucofuranosides or galactofuranosides. This behaviour suggests the presence of a pyranose ring in the non-reducing end. By treatment with an enzyme preparation, which hydrolysed methyl α-L- and to a smaller extent β-L-fucopyranoside,[5] fucose was easily liberated from each disaccharide. The strongly negative optical rotation of all the disaccharides indicates that the fucose molecules are joined in the α-configuration, and the similarity of the rotations points to the probable identity of their ring structures. Moreover, from the known optical rotations of the methyl fucopyranosides [6] and fucofuranosides,[7] it appears that the $2B$ values for furanose and pyranose rings are respectively $+850°$ and $-32{,}500°$, while the mean $2A$ value for fucosides lies around $-38{,}380°$. The molecular-rotation values of the three fucobi-itols fall between $-35{,}000°$ and $-38{,}600°$. On the reasonable assumption that the aglycone group should have a minor influence on the partial rotation of the anomeric carbon atom of the cyclic structure, only an α-pyranose ring can closely fit Hudson's isorotation rules. The results of periodate oxidation, in good

[1] Conchie and Percival, *J.*, 1950, 827.
[2] O'Neill, *J. Amer. Chem. Soc.*, 1954, **76**, 5074.
[3] Côté and Morgan, *Nature*, 1956, **178**, 1171.
[4] Bacon and Edelman, *Biochem. J.*, 1951, **48**, 174.
[5] Clancy, personal communication.
[6] Hockett, Phelps, and Hudson, *J. Amer. Chem. Soc.*, 1939, **61**, 1658.
[7] Watkins, *J.*, 1955, 2054.

agreement with the general conclusions reached by Hough and Perry,[9] support these deductions and confirm the positions of the linkages. The periodate–benzidine spray [9] can be useful in indicating a particular structural feature. The white spots left on the blue background by the benzidine spray appear as bright-yellow fluorescent areas under ultraviolet light in the instances of 1 : 2-fucobiose, 2-acetamido-2-deoxyglucose, 1 : 3-fucobi-itol, and maltitol, but not of methyl galactofuranoside under the usual conditions: such compounds are susceptible to a quick degradation to a substituted malondialdehyde (or a hemiacetal form of it).

Disaccharide (A) is 2-*O*-α-L-fucopyranosyl-L-fucose. Besides a very low copper reducing value, it has a low M_G value,[10] as has 2-*O*-methyl-L-fucose, and gives a negative test with triphenyltetrazolium chloride,[11,12] properties which are consistent with substitution on $C_{(2)}$. This structure is also indicated by the overoxidation which occurs with periodate (>7 mols. consumed with liberation of 5 mols. of formic acid after 48 hr.), whereas, after reduction, only one mol. of acetaldehyde was released and no formaldehyde (44 hr.).

Disaccharide (B), 3-*O*-α-L-fucopyranosyl-L-fucose, gives a positive triphenyltetrazolium chloride test and has a much higher M_G value than (A) or (C) (3-*O*-methyl-L-fucose has also a high M_G value), which suggests a 1 : 3-linkage. After treatment with periodate for a limited time, 5-deoxy-L-lyxose was liberated by hydrolysis of the oxidised disaccharide, which indicates a relatively resistant 1 : 3-linkage.[13] As was expected for such a structure, the corresponding alcohol was overoxidised by periodate to yield 1·5 mols. of acetaldehyde and one of formaldehyde (44 hr.).

Disaccharide (C) is 4-*O*-α-L-fucopyranosyl-L-fucose. The compound has a low M_G value, but it produces a positive triphenyltetrazolium chloride test which may be due to a 1 : 4-linkage. It reduced up to 3·8 mols. of periodate, and released 2·4 mols. of formic acid (48 hr.); after reduction, the product consumed just under 4 mols. of periodate, yielding no acetaldehyde but one mol. of formaldehyde and nearly 2 mols. of formic acid (44 hr.). This behaviour can only be explained by a non-reducing pyranose ring 1 : 4-linked to the reducing unit.

The fucobi-itols, which are rapidly separated from the bioses by ionophoresis, are not readily distinguished from each other under these conditions as they have similarly high M_G values, although the net charges in each case should result from different complexes. However, a clear distinction between these alcohols can be obtained by paper chromatography with Rees and Reynolds's mixture which was elaborated to separate glucose and sorbitol,[14] and its use here allows a further check on the homogeneity of the preparations. While sugar alcohols show unpredictable R_F values with the usual solvent systems, they often have much higher R_F values than those of the parent sugars when Rees and Reynolds's solvent system is used. Such behaviour is probably due mainly to one component of the mixture, boric acid, which can form complexes in a different way with a sugar and its reduced form. Maltose (or lactose) has no appreciable effect on the conductivity of boric acid solutions because no furanose forms are possible,[15] and this would explain the remarkable enhancement of R_F between maltitol and maltose, maltotri-itol, and maltotriose.[16] Similarly, a large difference in R_F has been observed between 1 : 4-fucobi-itol and 1 : 4-fucobiose, which have R_F values in the ratio of 2·9 while the ratio is 1·5 and 1·3 for the corresponding 1 : 2- and 1 : 3-pairs. Moreover, 5-deoxy-L-lyxitol has approximately the same R_F as 5-deoxy-L-lyxose, but ribitol, which has a very low effect on the conductivity

[9] Hough and Perry, *Chem. and Ind.*, 1956, 768.
[9] Cifonelli and Smith, *Analyt. Chem.*, 1954, **26**, 1132.
[10] Foster, *J.*, 1953, 952.
[11] Wallenfels, *Naturwiss.*, 1950, **37**, 491.
[12] Bell and Dedonder, *J.*, 1954, 2866.
[13] Barker and Smith, *Chem. and Ind.*, 1952, 1035.
[14] Rees and Reynolds, *Nature*, 1958, **181**, 767.
[15] Böeseken, *Adv. Carbohydrate Chem.*, 1949, **4**, 189.
[16] Walker and Whelan, *Biochem. J.*, 1957, **67**, 548.

of boric acid solutions,[15] does not show a large increase in R_F and runs even more slowly than ribose (which has a strong tendency to exist in furanose forms) under those conditions.

The present findings can, with reservations, contribute to a structural study of fucoidin. The " linkage analysis method " [17] does not always give a fair estimate of the ratios of the different units present. The fragments released cannot always be recovered quantitatively, as complete purification of the products can result in losses which vary with the fractionation procedures used. Moreover, the hydrolytic conditions for maximum yields vary according to the sugars and their linkages. For instance, fucose is rather quickly split off from some materials by N-acetic acid at 100°;[3,18,19] the fucobioses (and fucobi-itols) are also easily hydrolysed and, apparently, at different speeds. However, the relative rates of acetolysis may not be the same, and, moreover, a sulphate group is present in fucoidin. The presence of oligosaccharides in minor quantities after acid-treatment can also be due to reversion, which is usually characterised[20,21] by the predominance of products arising by condensation at the most reactive position (although the proportions between synthesis and hydrolysis through reversion might sometimes differ), with a minority of other complex structures. It is possible to produce fucose disaccharides by acid reversion and the three types mentioned above have been detected after such a process, the 1 : 2-α-biose being predominant owing to the great reactivity of $C_{(2)}$. However, the conditions used in acetolysis differ greatly from those suitable for extensive reversion, which results in a very complex mixture. Finally, the homogeneity of polysaccharide preparations is not easily proved in a satisfactory way and the detection of a variety of linkages even in a sample made up of a single type of sugar requires confirmation by isolation of larger fragments which embody more than one type of linkage or by a careful methylation.

The first knowledge about the arrangement of fucose units in fucoidin was obtained by methylation. Conchie and Percival [1] isolated 3-*O*-methyl-L-fucose as a major component (*ca.* 60%) after hydrolysis of methylated fucoidin and suggested that the main residue is made up of 1 : 2-pyranose units carrying a 4-sulphate group, as alkali would lead to the elimination of sulphate from position $C_{(2)}$ or $C_{(3)}$ (vicinal *trans*-hydroxyl). The α-configuration was suggested because of the strong lævorotation of this polysaccharide. These conclusions were confirmed by O'Neill who, on the basis of periodate oxidation, characterised the fucobi-itol isolated as 2-*O*-α-L-fucopyranosyl-L-fucoitol, the α-configuration again being inferred from the highly negative rotation. The present work has led to the isolation and identification of the corresponding biose. To explain the presence of free fucose after methylation, Conchie and Percival suggested, without excluding the possibility of an incomplete methylation, the presence of branching points at $C_{(3)}$ on the main (2-linked) residue, or the presence of fucose molecules with two sulphate groups. The branching points, if any, can represent only a minor fraction of the linkages and the presence of 1 : 3-disaccharide units in the acetolysate is in line with this as the yield was small (though no attempt was made to improve it). Alternatively, it could mean branching points on 1 : 4-units, carrying a 2-sulphate group, as the present work affords strong evidence for the occurrence of many 1 : 4-linkages in fucoidin. The possibility cannot be rejected that these two main kinds of linkage, 1 : 2 and 1 : 4, might arise here from different polysaccharides present together in various proportions. This aspect was not investigated by us, but it is noteworthy that O'Neill noticed two components on electrophoresis of a purified sample of fucoidin.[2] Conchie and Percival pointed to the presence of 1 : 4-linkages as a chain of the general structure of fucoidin, having cautiously described their last fraction of methylated fucoidin (*ca.* 20%; $[\alpha]_D$ +4·6°) as 2 : 3-di-*O*-methyl-L-fucose after the preparation of suitable derivatives. Schmidt and Wernicke [22] had, however,

[17] Peat, Whelan, and Edwards, *J.*, 1955, 355.
[18] Kuhn, Baer, and Gauhe, *Chem. Ber.*, 1955, **88**, 1135.
[19] Aminoff, Morgan, and Watkins, *Biochem. J.*, 1950, **46**, 426.
[20] Jones and Nicholson, *J.*, 1958, 27; Ball and Jones, *ibid.*, p. 33.
[21] Thompson, Anno, Wolfrom, and Inatome, *J. Amer. Chem. Soc.*, 1954, **76**, 1309.
[22] Schmidt and Wernicke, *Annalen*, 1944, **556**, 179.

synthesised 2 : 3-di-*O*-methyl-D-fucose with $[\alpha]_D$ +73°, and recently Gardiner and Percival have reported $[\alpha]_D$ −97° for the L-isomer obtained by partial methylation.[23] Thus this fraction from methylated fucoidin remains largely unidentified and, according to other data, the contaminant(s) in it would not be any of the fucofuranose dimethyl ethers with positive optical rotation.[23] Since even N-sodium hydroxide at 100° could remove appreciable amounts of sulphate from fucoidin,[1] the positive optical rotation could be explained by the presence of a methylated fucose epimer produced by Walden inversion [24] on removal of the sulphate group on 1 : 4-linked units during methylation. The small quantity of dimethylfucose obtained might also have been produced by terminal non-reducing fucose molecules with a (stable) 4-sulphate group. As regard the minor features of fucoidin, glucose, galactose, etc., are probably constituents of contaminating polysaccharides. The probable isolation of 3-*O*-methyl-L-fucose from crude fucoidin [25] has not been confirmed (see p. 2252). That methylated L-fucose occurs naturally has been recently suggested by the isolation of 2-*O*-methyl-L-fucose from plum leaf [26] and possibly another plant.[25]

Experimental

General Methods.—Adsorption chromatography was carried out with different preparations of charcoal: (1) B.D.H., "acid-washed," with moderate adsorptive power; (2) Hopkin and Williams, that was treated successively with boiling 20% acetic acid for 1 hr., washed with water and hot aqueous ethanol (25%), and dried at 150° in air. The latter material was a strong adsorbent even for fucose. For use, either type of charcoal was mixed with washed Celite (1 : 1, w/w) and elution was with aqueous ethanol.[27]

Preparative paper chromatography by the descending technique was usually made with Whatman sheets no. 17 (18½ × 22½ in.), which can easily accommodate 0·5 g. of material each. Glass rods were fixed to provide a smooth bend to the sheets, which were clamped one on each side of a stainless steel frame dipping into the solvent contained in a 1-l. trough. This very thick paper offers a great rate of flow and is at the same time reasonably even. After detection, elution of the sugar bands was made either by sewing on strips of Whatman no. 3 mm. as wicks for descending technique [28] or by pulping the strips in a Waring blender. Whatman paper no. 1 was used for qualitative chromatography by the descending technique. The following solvent systems were used: (*a*) butan-1-ol–pyridine–water (3 : 1 : 1, v/v),[29] (*b*) butan-1-ol–acetic acid–water (4 : 1 : 5, v/v),[30] and (*c*) ethyl methyl ketone–acetic acid–water saturated with boric acid (9 : 1 : 1, v/v).[14] The spraying reagents were benzidine–trichloroacetic acid,[4] triphenyltetrazolium chloride,[11] and benzidine–periodate.[9]

Ionophoresis was carried out with an apparatus of the type described by Foster,[31] used as a semi-open one by insertion of a suitable rubber gasket between the glass plates. The paper (no. 3MM, 57 cm. in length) was dipped completely in the buffer before being put between the plates for draining and spotting. To allow long runs (5 v/cm., 15 hr.), the starting line was placed 25 cm. from the cathode side. M_G values were measured, as by Foster, in presence of Sørensen's borate buffer (pH 10) (*viz.*, 7·44 g. of boric acid in 1 l. of 0·1N-sodium hydroxide). Non-reducing materials were detected with the benzidine–periodate spray [8] after the dried paper had been first treated by acetone containing 5% of acetic acid.

Oxidations were made in the dark at room temperature in 0·2M-sodium metaperiodate. Periodate consumption was measured by iodometry at pH 7 [32] or in acid medium,[33] formic acid by iodometry, formaldehyde by chromotropic acid,[34] and acetaldehyde by piperazine–sodium

[23] Gardiner and Percival, *J.*, 1958, 1414.
[24] Peat, *Adv. Carbohydrate Chem.*, 1946, **2**, 38.
[25] Springer, "Chemistry and Biology of Mucopolysaccharides," Ciba Foundation Symposium, Churchill, London, 1958, p. 216.
[26] Anderson, Andrews, and Hough, *Chem. and Ind.*, 1957, 1453.
[27] Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677.
[28] Brownell, Hamilton, and Casselman, *Analyt. Chem.*, 1957, **29**, 550.
[29] Hough, Jones, and Wadman, *J.*, 1950, 1702.
[30] Partridge, *Biochem. J.*, 1948, **42**, 238.
[31] Foster, *Chem. and Ind.*, 1952, 1050.
[32] Neumüller and Vasseur, *Arkiv Kemi*, 1953, **5**, 235.
[33] Hughes and Nevell, *Trans. Faraday Soc.*, 1948, **44**, 941.
[34] Frisell, Meech, and Mackenzie, *J. Biol. Chem.*, 1954, **207**, 709.

nitroprusside.[35] Reductions were by sodium borohydride,[36] and boric acid was removed by methanol in the usual way after de-ionisation by resins.

The degree of polymerisation was measured in a manner similar to that described by Peat, Whelan, and Roberts.[37] As fucitol produces a negligible colour, the ratios of fucose in the compounds before and after reduction can be measured by Dische and Shettles's method for methylpentoses, which was used, as modified by Gibbons,[38] with samples of 1 : 2- and 1 : 4-fucobiose previously treated according to Peat *et al.*[37] The average values were 2·05 and 2·00 for the 1 : 2- and 1 : 4-bioses respectively. Determination of fucose is possible in the usual range (10—50 μg.), as the inhibiting effect of inactivated sodium borohydride on the development of colour is small. With the third substance (1 : 3-linkage), the ratio of fucose to fucitol was directly measured. A pure sample (*ca.* 3 mg.) of the fucobi-itol was hydrolysed by N-acetic acid and spotted on paper (solvent *c*), and the bands corresponding to fucose and fucitol were eluted. Aliquot parts equivalent to 70—130 μg. of acetaldehyde were treated by 0·05M-periodate in phosphate buffer (pH 7, 90 min., 25°), and acetaldehyde was measured as before. The net values obtained from the fucose and fucitol levels had a ratio of 1·10, while uniform and low blanks were shown with a control sheet of paper identically treated.

Hydrolysis of the disaccharides as 1—2% solutions in N-acetic acid at 100° was followed by paper chromatography which indicated 75% hydrolysis in ~2 hr. for the 1 : 2-biose, in ~9 hr. for the 1 : 3-biose, and ~7 hr. for the 1 : 4-biose.

All solutions were concentrated under reduced pressure at <20° in a rotary evaporator with a seal provided by two glass tubes ground into each other, the mobile one (diam. 15 mm.) being set in a self-aligning ball-bearing. Optical rotations were measured in water at 22°.

Acetolysis and Fractionation of Fucoidin.—A commercial sample of fucoidin, prepared from *F. vesiculosus* as described by Black, Dewar, and Woodward,[39] dried at 50° *in vacuo* for 36 hr., contained 35% of fucose [38] and had $[\alpha]_D$ −93° (*c* 1). Complete hydrolysis showed the presence of small amounts of glucose, mannitol (chromatographic evidence after development with solvent *c*), xylose (identified by its R_F and M_G), galactose, mannose (?), and uronic acid(s). A fast component had R_F similar to that of 3-*O*-methylfucose in solvent *b*, but of quite different M_G. A first batch (25 g.) was acetolysed and deacetylated by O'Neill's method.[2] After neutralisation, the solution was freed from methanol by evaporation, diluted to 600 ml. with water, and fractionated by the frontal analysis method [40] as follows: Four Celite–charcoal (no. 2) filters of 30 ml., separated by 2 cm., were set up on top of each other in a glass tube (diam. 2·5 cm.). The sugar solution was percolated through this column and followed by 200 ml. of water. Each section was extruded and eluted with 25% ethanol. The bottom filter (IV) was saturated with fucose, the one above (III) contained mainly disaccharide (C), the second filter retained mostly disaccharide (A) (on first evidence), and the top section contained various components. Combined eluates from (I) and (II) were spotted on Whatman paper no. 17 which was irrigated for 30 hr. with solvent *a*. The syrup recovered after elution and usual purification was dissolved in moist methanol, from which crystals of disaccharide (A) separated quickly (0·15 g.). On addition of ethyl acetate, the mother-liquors yielded some more material, shown to be a mixture of disaccharides (A) and (B). Disaccharide (A) has $[\alpha]_D$ −160° (0·5 hr.) ⟶ −169° (*c* 1) and m. p. 185—190° (decomp.), M_G 0·34, R_{fuc} 0·78, 0·74, 0·45 in solvents *a*, *b*, and *c* respectively (galactose has 0·56, 0·51, and 0·38). With the benzidine spray, it produces a yellow-orange colour. Acid-hydrolysis of the corresponding fucobi-itol, which crystallised easily from moist ethanol, liberated fucose and fucitol, which are readily distinguishable with all solvents used: fucitol has R_{fuc} 1·2, 1·3, and 2·4 in solvents *a*, *b*, and *c* respectively. The fucobi-itol has $[\alpha]_D$ −124° (*c* 1), m. p. 191—192° (lit.,[2] $[\alpha]_D$ −118°, m. p. 190—192°), M_G 0·59, R_{fuc} 0·79, 0·78, and 0·68 in solvents *a*, *b*, and *c* respectively, and is identical (mixed m. p. and R_F in solvent *c*) with the fucobi-itol isolated by O'Neill. The contents of filter (III) were similarly purified by partition with solvent *a* (40 hr.), disaccharide (C) being obtained as a semi-amorphous product by precipitation with ethyl acetate from methanol (0·10 g.) (see below).

A second acetolysis was carried out as before, with another sample of fucoidin (50 g.). After

[35] Fromageot and Heitz, *Mikrochim. Acta*, 1938, **3**, 52.
[36] Abdel-Akher, Hamilton, and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 4691.
[37] Peat, Whelan, and Roberts, *J.*, 1956, 2258.
[38] Gibbons, *Analyst*, 1955, **80**, 268.
[39] Black, Dewar, and Woodward, *J. Sci. Food Agric.*, 1952, **3**, 122.
[40] Tiselius, *Kolloid Z.*, 1943, **105**, 101.

deacetylation with barium methoxide at 0° for 48 hr. and neutralisation, methanol was removed and the filtered solution diluted to 1500 ml. with water. The solution was passed through two filters of charcoal (no. 2)–Celite (180 and 70 ml.) which were washed with water (900 ml.). The smaller filter contained only fucose (*ca.* 0·45 g.). From the first filter, about 1·5 g. of material (containing a trace of fucose) with similar elution properties were collected in a volume of 400 ml. by displacement analysis [40] with a 0·5% solution of raffinose in 15% ethanol. The mixture was refractionated on a charcoal (no. 2)–Celite column (150 ml.) with a gradient elution [41] $x = 25\%$, $v = 1$ l. The first peak, at 10% ethanol, was due to disaccharide (C), the purification of which was completed by partition on a-Celite column [42] (300 g.; diam. 5 cm.) with 5 l. of solvent. The sugar was located by spraying a print taken on the extruded column with a no. 3MM paper strip and recovered after elution as described previously (0·47 g.). Heating *in vacuo* at 76° caused the material to lose weight equivalent to one mol. of water, and the final product was a semi-amorphous solid (according to a *X*-ray diffraction photograph), $[\alpha]_D$ −170° (*c* 1). It has M_G 0·28, R_{fuc} 0·64, 0·62, and 0·28 in solvents *a*, *b*, and *c* respectively, and gives a bright yellow spot with benzidine. The corresponding alcohol (amorphous) has $[\alpha]_D$ −115° (*c* 1), M_G 0·62, R_{fuc} 0·79, 0·77, and 0·82 in solvents *a*, *b*, and *c*. Hydrolysis by acetic acid afforded fucose and fucitol.

The second peak eluted from the charcoal column was mainly a mixture of disaccharides (A) and (B). Small amounts of contaminants with clearly different R_F were first eliminated by partition chromatography on Whatman paper no. 17 (solvent *a* for 28 hr.). The final syrup (*ca.* 0·30 g.) was fractionated on a charcoal (no. 1)–Celite filter (75 ml.) in the presence of 0·025M-sodium tetraborate [43] (pH 9·2) with a gradient of ethanol, $x = 10\%$, $v = 1$ l. Disaccharide (B) started to come from the column at about 2½% ethanol and was clearly separated from disaccharide (A). Each pool was run through a column of Zeo-Karb 225 (H^+), the effluent being freed from boric acid as usual. Disaccharide (A) (0·12 g.) crystallised from methanol. Disaccharide (B) had to be further purified by paper chromatography on Whatman paper no. 3MM with solvent *b* and passed through a small charcoal column. The final syrup crystallised slowly in presence of ethanol (0·06 g.), then having m. p. 198—200°, $[\alpha]_D$ −200° ⟶ −191° (*c* 1). Disaccharide (B) produces a yellow-brown colour with the benzidine spray and has M_G 0·52, R_{fuc} 0·80, 0·75, and 0·43 in solvents *a*, *b*, and *c*. The corresponding fucobi-itol (a syrup) had $[\alpha]_D$ −112° (*c* 1), M_G 0·60, R_{fuc} 0·75, 0·74, and 0·56 in solvents *a*, *b*, and *c*, and also gave fucose and fucitol on acid-hydrolysis. The fucobiose was oxidised by periodate (5-fold excess) at 0° for 90 min.; after de-ionisation and hydrolysis by 0·1N-hydrochloric acid for 3 hr. 5-deoxylyxose was identified on paper chromatograms.

5-Deoxy-L-lyxose.—L-Fucose was treated with bromine in presence of calcium carbonate, and the non-reducing solution run successively through columns of Zeo-Karb 225 (H^+ form) and DeAcidite E (AcO^- form); L-fuconolactone, obtained on evaporation of the final effluent, was transformed into L-fuconamide as described by Clark.[44] Weerman degradation of this product led to 5-deoxy-L-lyxose,[45] but several non-reducing materials were also detected by chromatography in the final syrup. The mixture, in phosphate buffer (pH 7·5), was fractionated on charcoal (no. 2)–Celite and then by partition on Celite (water-saturated butanol), to yield 5-deoxy-L-lyxose as a chromatographically pure syrup (yield, 8%). As a result of observations on the oxidation of monosaccharides by periodate,[46,47] this methyltetrose was also obtained by oxidation of L-fucose with one equivalent of periodate at room temperature. After de-ionisation and hydrolysis, unchanged fucose (*ca.* 50%) was removed by partition chromatography on Whatman paper no. 17 (water-saturated butanol for 20 hr.) and the material was finally purified by chromatography on charcoal (yield, 5%). 5-Deoxy-L-lyxose has $[\alpha]_D$ −35° (*c* 1) (lit.,[48] $[\alpha]_D$ +32° for 5-deoxy-D-lyxose), M_G 0·78, R_{fuc} 1·7 in solvents *a* and *b*. With benzidine spray, it gives a brownish-red spot, strongly fluorescent in ultraviolet light; treatment on paper with the Ehrlich reagent at 80° produces an orange-purple spot which distinguishes it from other oxidation products of fucose.

[41] Alms, Williams, and Tiselius, *Acta Chem. Scand.*, 1952, **6**, 826.
[42] Lemieux, Bishop, and Pelletier, *Canad. J. Chem.*, 1956, **34**, 1365.
[43] Barker, Bourne, and Theander, *J.*, 1955, 4276.
[44] Clark, *J. Biol. Chem.*, 1922, **54**, 65.
[45] Schmidt, Mayer, and Distelmaier, *Annalen*, 1943, **555**, 26.
[46] Courtois and Guernet, *Bull. Soc. chim. France*, 1957, 1388.
[47] Warsi and Whelan, *Chem. and Ind.*, 1958, 71.
[48] Votoček and Valentin, *Coll. Czech. Chem. Comm.*, 1930, **2**, 36; *Chem. Zentr.*, 1930, I, 2543.

XUM

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445. *Internuclear Cyclisation. Part XIV.* Reactions with Hydroaromatic Rings.*

By D. H. HEY and R. A. J. LONG.

Catalytic decomposition of the diazonium salts from ethyl *o*-amino-α-*cyclo*hexenylcinnamate (I; R = Et, R′ = H) and ethyl *o*-amino-α-2-methyl-*cyclo*hexenylcinnamate (I; R = Et, R′ = Me) (or the free acid) gave derivatives of tetrahydrophenanthrene, which were identified by conversion into phenanthrene and 1-methylphenanthrene respectively. These reactions provide the first examples of internuclear cyclisation of this type involving a hydroaromatic ring. Similar reactions with tetra- and hexa-hydrobenzoyl-*N*-methyl-*o*-phenylenediamine gave indeterminate results.

ALTHOUGH numerous reactions involving diazo-compounds have been recorded in which internuclear cyclisation has been effected with a variety of homocyclic and some heterocyclic aromatic compounds,[1,2] no attempts appear to have been reported in which the cyclisation involves a non-aromatic ring. Such reactions would yield partially reduced systems, which are difficult of access by other methods, and might provide valuable evidence on the mechanism of the ring closure.

It has been shown by Schwenk and Papa [3] that *cyclo*hex-1-enylacetic acid and aromatic aldehydes give *cyclo*hexenylcinnamic acids. By this method condensation with *o*-nitrobenzaldehyde in the presence of triethylamine gave α-*cyclo*hex-1-enyl-*o*-nitrocinnamic acid, which was esterified and reduced to ethyl *o*-amino-α-*cyclo*hex-1-enylcinnamate (I; R = Et, R′ = H). The derived diazonium fluoroborate decomposed in acetone in the presence of copper powder to give ethyl 5 : 6 : 7 : 8-tetrahydrophenanthrene-9-carboxylate (II; R = Et, R′ = H) in 50% yield. This ester was hydrolysed to the acid (m. p. 210°), which gave phenanthrene (III; R′ = H) on dehydrogenation and decarboxylation. A similar result was obtained when the aqueous diazonium sulphate was decomposed at room temperature by the addition of copper powder. After this work was completed a different preparation of the tetrahydrophenanthrenecarboxylic acid was reported by Kristensen and Cordier [4] who recorded the same melting point.

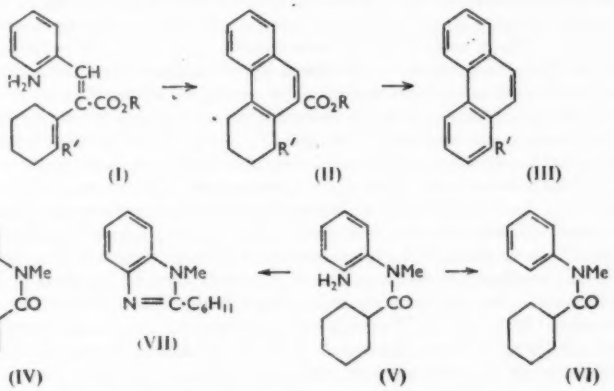
Similarly 2-methyl*cyclo*hexenylacetic acid and *o*-nitrobenzaldehyde gave α-2-methyl-*cyclo*hexenyl-*o*-nitrocinnamic acid, its ethyl ester, and the amino-ester (I; R = Et, R′ = Me). The derived diazonium chloride decomposed in water at room temperature on addition of copper powder and hydrolysis of the product gave 5 : 6 : 7 : 8-tetrahydro-8-methylphenanthrene-9-carboxylic acid (II; R = H, R′ = Me). The same acid was obtained from the diazonium chloride prepared from *o*-amino-α-2-methyl*cyclo*hexenylcinnamic acid (I; R = H, R′ = Me). The structure of the tetrahydro-acid was confirmed by dehydrogenation and decarboxylation to 1-methylphenanthrene (III; R′ = Me). The formation of tetrahydrophenanthrenes in this manner provides the first examples of a ring closure of

* Part XIII, *J.*, 1959, 1563.

[1] Leake, *Chem. Rev.*, 1956, **56**, 27.
[2] De Tar, "Organic Reactions," J. Wiley and Sons, Inc., New York, 1957, Vol. IX, p. 409.
[3] Schwenk and Papa, *J. Amer. Chem. Soc.*, 1945, **67**, 1432.
[4] Kristensen and Cordier, *Compt. rend.*, 1956, **242**, 908.

this type with a hydroaromatic system. They also show that the Perkin-type condensations with *cyclo*hexenylacetic acid and the aromatic aldehyde give the substituted cinnamic acid in which the carboxyl (ethoxycarbonyl) and nitrophenyl groups are in a *trans*-relation. The actual ring closure probably involves reaction at the α-methylenic position in the *cyclo*hexene ring and as such is in agreement with the representation of the copper-catalysed reaction as a homolytic process. The work of Waters [5] and of Farmer and Michael [6] has shown that the α-methylenic position in *cyclo*hexene is readily attacked by free radicals.

The inability to obtain *cyclo*hexylcinnamic acids by Schwenk and Papa's method [3] made it necessary to turn to the phenanthridone series in order to investigate the behaviour in the internuclear cyclisation of a fully reduced ring system. Before proceeding to the hexahydro-series, we prepared *N*-tetrahydrobenzoyl-*N*-methyl-*o*-nitroaniline and reduced it to the amine but catalytic decomposition of the aqueous diazonium chloride prepared from the amino-amide (IV) gave no pure products. On the other hand, reduction of *N*-hexahydrobenzoyl-*N*-methyl-*o*-nitroaniline gave *N*-hexahydrobenzoyl-*N*-methyl-*o*-phenylenediamine (V), which on diazotisation and treatment with copper powder gave *N*-hexahydrobenzoyl-*N*-methylaniline (VI) and an oil which, on the evidence of its infrared spectrum, appeared to contain a carbonyl group. The oil did not appear to contain *N*-methyl-2-oxo*cyclo*hexanecarboxyanilide, which was prepared by Sheehan, Goodman, and Hess's



method [7] using *NN*-di*cyclo*hexylcarbodi-imide for comparison. The application of Sheehan, Goodman, and Hess's method to the preparation of *N*-tetrahydrobenzoyl-*o*-nitroaniline failed, the only products isolated being *NN*-di*cyclo*hexylurea and *N*-tetrahydrobenzoyl-*NN*-di*cyclo*hexylurea (cf. Schulz and Fiedler [8]). When *N*-hexahydrobenzoyl-*N*-methyl-*o*-phenylenediamine (V) was treated in ether with dry hydrogen chloride 2-*cyclo*hexyl-1-methylbenzimidazole (VII) was formed.

Experimental

Ethyl α-cyclo*Hex*-1-*enyl*-o-*nitrocinnamate*.—Anhydrous triethylamine (10·1 g.) and acetic anhydride (51 g.) were added to *cyclo*hex-1-enylacetic acid (14 g.; prepared in 50% yield by Schwenk and Papa's method; [3] m. p. 37°) and *o*-nitrobenzaldehyde (15·1 g.) with stirring, under reflux, and the whole was heated for 12 hr. at 105—110° in dry nitrogen. The mixture was cooled to 60° and the excess of acetic anhydride was decomposed with water. The mixture was

[5] Waters, *J.*, 1939, 1805.
[6] Farmer and Michael, *J.*, 1942, 513.
[7] Sheehan, Goodman, and Hess, *J. Amer. Chem. Soc.*, 1956, **78**, 1368.
[8] Schulz and Fiedler, *Chem. Ber.*, 1956, **89**, 2681.

then poured on ice, and the semi-solid product was extracted with ether. The extract was washed with water and 5% aqueous sodium carbonate. The alkaline washings were freed from ether, and the hot solution was neutralised with 2N-hydrochloric acid. The neutral solution was heated on a boiling-water bath for 30 min. with charcoal, after which it was filtered and acidified. Recrystallisation of the precipitated acid from aqueous ethanol gave α-cyclo*hex*-1-*enyl*-o-*nitrocinnamic acid* (12 g.) in pale yellow needles, m. p. 121° (Found: C, 65·8; H, 5·6. $C_{15}H_{15}O_4N$ requires C, 66·0; H, 5·5%). By the Fischer method the acid (9·9 g.) gave the *ethyl ester* (7 g.), needles (from aqueous ethanol), m. p. 37·5° (Found: C, 67·8; H, 6·3; N, 4·6. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·3; N, 4·7%).

Ethyl o-*Amino*-α-cyclo*hex*-1-*enylcinnamate Hydrochloride*.—A mixture of the above ethyl ester (2 g.) and the stannous chloride reagent (20 ml.), prepared as described by Thiele and Dimroth,[9] was gently warmed for a few minutes and then left at room temperature for 3 hr. The yellow complex which separated was treated with an excess of 2N-aqueous sodium hydroxide until the tin salts had dissolved, leaving the free amine as an oil. The base was extracted with ether, and dry hydrogen chloride was passed into the dried (Na_2SO_4) ethereal solution. The *hydrochloride* separated and crystallisation from ether–ethanol gave needles (1·5 g.), m. p. 151° (Found: C, 66·0; H, 6·8; N, 4·4. $C_{17}H_{21}O_2N,HCl$ requires C, 66·4; H, 7·2; N, 4·3%).

Decomposition of the Diazonium Fluoroborate prepared from Ethyl o-*Amino*-α-cyclo*hex*-1-*enylcinnamate*.—A suspension of the above hydrochloride (3·5 g.) in concentrated hydrochloric acid (20 ml.) and water (60 ml.) was diazotised by sodium nitrite (4 g.) in water (15 ml.). The solution was kept at 0° and filtered. Sodium fluoroborate (5 g.) in water (15 ml.) was added slowly at 0° and the yellow precipitate of the diazonium fluoroborate was collected and dried overnight *in vacuo*. Copper powder (3 g.) was added to a suspension of the dry fluoroborate (2·8 g.) in acetone (200 ml.). There was immediate evolution of nitrogen: the solution was left at room temperature for 3 hr., then warmed and filtered into water, the insoluble residue being extracted several times with acetone and hot water. The combined filtrate and extracts were extracted several times with chloroform. The chloroform solution was washed with 10% aqueous sodium hydroxide and with water and dried (Na_2SO_4). Removal of the chloroform under reduced pressure left a residue (1·8 g.), which was adsorbed from 1 : 1 benzene–light petroleum (b. p. 60—80°) on an alumina column (100 g.). Elution with 1 : 1 benzene–light petroleum (b. p. 60—80°) (350 ml.) gave ethyl 5 : 6 : 7 : 8-tetrahydrophenanthrene-9-carboxylate (1·48 g.) as a low-melting solid. Further elution with the same solvent, benzene, ether, and ethanol gave only small quantities of gums. Acidification of the alkaline washings gave a trace of tar. The ethyl ester (1·4 g.) in ethanol (5 ml.) was boiled under reflux for 4 hr. with 10% aqueous potassium hydroxide (50 ml.). The cold solution was washed with ether and acidified with concentrated hydrochloric acid. The acid solution was extracted several times with ether and concentration of the dried (Na_2SO_4) extract deposited 5 : 6 : 7 : 8-*tetrahydrophenanthrene*-9-*carboxylic acid* (1·0 g.), which crystallised from aqueous ethanol in plates, m. p. 210° (Found: C, 79·2; H, 6·2. $C_{15}H_{14}O_2$ requires C, 79·6; H, 6·2%), $\lambda_{max.}$ 237, 285, 330—335 mμ (log ε 4·73, 3·76, 3·15). A portion of the acid (0·5 g.) was heated with 30% palladium–charcoal (0·2 g.) in a molecular micro-still at 300° for 30 min. Crystallisation of the white sublimate from alcohol gave phenanthrene (0·3 g.) in plates, m. p. and mixed m. p. 100° (picrate, m. p. and mixed m. p. 143—144°).

Decomposition of the Diazonium Sulphate prepared from Ethyl o-*Amino*-α-cyclo*hex*-1-*enylcinnamate*.—A suspension of the ester (1·1 g.) in sulphuric acid (5 ml.) and water (30 ml.) was diazotised with sodium nitrite (1 g.) in water (10 ml.) at 0°. After 90 min., the mixture was diluted with water (200 ml.), the yellow diazonium sulphate which had separated redissolving. Urea (2 g.) was added and then copper powder (2 g.), after which the mixture was stirred for 3 hr. at room temperature. The mixture was left overnight and the brown solid which had separated was filtered off. Both filtrate and residue were extracted with ether, and the solvent was removed under reduced pressure from the combined extracts. The residual brown oil was boiled under reflux for 4 hr. with 10% alcoholic potassium hydroxide, after which the solution was diluted with water (400 ml.) and washed with ether. The alkaline solution was neutralised with concentrated hydrochloric acid and heated for 30 min. on a boiling-water bath with charcoal. Filtration and acidification gave 5 : 6 : 7 : 8-tetrahydrophenanthrene-9-carboxylic acid (0·2 g.) in plates, m. p. and mixed m. p. 209—210° (from dilute ethanol).

α-2-*Methyl*cyclo*hex*-1-*enyl*-o-*nitrocinnamic Acid*.—Ethyl 2-methyl*cyclo*hex-1-enylacetate,

[9] Thiele and Dimroth, *Annalen*, 1899, **305**, 114.

prepared in 56% yield by the general method of Schwenk and Papa,[9] had b. p. 110—111·5°/14 mm. in agreement with Chuang, Tien, and Ma,[10] and hydrolysis with aqueous-alcoholic potassium hydroxide gave the free acid which solidified in ice (Kon and Thakur [11] recorded m. p. 10—14°). 2-Methyl*cyclo*hex-1-enylacetic acid (15·4 g.), *o*-nitrobenzaldehyde (15 g.), acetic anhydride (50 g.), and triethylamine (10 g.) were heated on a boiling-water bath in nitrogen for 25 hr., then worked up as described above, giving the acidic products as a brown solid (9 g.). Crystallisation from alcohol gave *o*-nitrocinnamic acid (2·3 g.), m. p. and mixed m. p. 244°. Dilution of the mother-liquor gave α-2-*methyl*cyclo*hex*-1-*enyl*-o-*nitrocinnamic acid* (5·5 g.), which separated from dilute ethanol in needles, m. p. 144° (Found: C, 66·7; H, 5·4. $C_{16}H_{17}O_4N$ requires C, 67·0; H, 5·9%).

Ethyl o-*Amino*-α-2-*methyl*cyclo*hex*-1-*enylcinnamate*.—The above nitro-acid (2 g.) was converted by boiling ethanol containing anhydrous hydrogen chloride into the ethyl ester, b. p. 138°/6 × 10^{-4} mm. This (2·0 g.) was reduced with the stannous chloride reagent [9] (30 ml.) as above. The amino-acid was extracted from ether with concentrated hydrochloric acid. The acid solution was then made alkaline with ice-cooling and extracted with ether. Removal of the ether from the dried extract gave the *amino-ester* (1·0 g.), b. p. 112—117°/6 × 10^{-4} mm. (Found: C, 75·9; H, 8·0. $C_{18}H_{23}O_2N$ requires C, 75·8; H, 8·1%).

o-*Amino*-α-2-*methyl*cyclo*hex*-1-*enylcinnamic Acid*.—The nitro-acid (1·5 g.) in ethanol (50 ml.) was reduced with hydrogen at atmospheric pressure in the presence of 5% palladium–charcoal (1·0 g.). After the requisite volume of hydrogen had been taken up, the solution was filtered and evaporated to small bulk under reduced pressure. Addition of water deposited o-*amino*-α-2-*methyl*cyclo*hex*-1-*enylcinnamic acid* (1·2 g.), which crystallised from dilute ethanol in yellow needles, m. p. 173° (Found: C, 75·1; H, 7·0. $C_{16}H_{19}O_2N$ requires C, 74·6; H, 7·4%).

Decomposition of the Diazonium Chloride from Ethyl o-*Amino*-α-2-*methyl*cyclo*hex*-1-*enylcinnamate*.—The amino-ester (0·82 g.) in concentrated hydrochloric acid (10 ml.) and water (30 ml.) was diazotised at 0° with sodium nitrite (0·5 g.) in water (20 ml.). The solution was stirred for 3 hr. at 0—5°, after which alcohol (40 ml.) was added and then copper powder (1·0 g.). The mixture was stirred over-night after which reaction with alkaline β-naphthol was negative. The mixture was filtered and both filtrate and residue were extracted with chloroform. The combined chloroform extracts were washed with dilute alkali, dried (Na_2SO_4), and evaporated to a dark oil (0·80 g.), which was chromatographed in 1 : 1 benzene–light petroleum (b. p. 60—80°) on alumina (80 g.). Elution with 1 : 1 benzene–light petroleum (b. p. 40—60°) (200 ml.) gave a white solid, which on hydrolysis with alcoholic potassium hydroxide gave 5 : 6 : 7 : 8-*tetrahydro*-8-*methylphenanthrene*-9-*carboxylic acid* (0·28 g.), plates (from methanol), m. p. 187° (Found: C, 79·9; H, 7·0. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%), $\lambda_{max.}$ 235, 285, 328—331 mμ (log ε 4·67, 3·76, 3·07). Further elution with 1 : 1 benzene–light petroleum (b. p. 40—60°) (200 ml.), ether (400 ml.), and alcohol (200 ml.) gave only gums. Acidification of the alkaline extract gave only a trace of tar.

Decomposition of the Diazonium Chloride from o-*Amino*-α-2-*methyl*cyclo*hex*-1-*enylcinnamic Acid*.—The amino-acid (1·0 g.) in concentrated hydrochloric acid (10 ml.) and water (20 ml.) was diazotised at 0—5° with sodium nitrite (0·4 g.) in water (20 ml.). The solution was diluted with water (200 ml.) and urea (0·4 g.) was added. The solution was filtered and to the filtrate copper powder (1·0 g.) was added. After being stirred for 2 hr. the mixture no longer gave a positive reaction with alkaline β-naphthol. The solution was filtered and both residue and filtrate were extracted with chloroform. The combined extracts were washed with 10% aqueous sodium hydroxide and the alkaline solution was neutralised and heated on the water-bath for 30 min. with charcoal. It was then filtered and acidified. The precipitated solid (0·4 g.) crystallised from ethanol to give 5 : 6 : 7 : 8-*tetrahydro*-8-*methylphenanthrene*-9-*carboxylic acid* (0·28 g.) in plates, m. p. 187° alone or on admixture with the acid obtained as above. Dehydrogenation and decarboxylation at 300° with palladium–charcoal as described above, and crystallisation of the sublimate from methanol gave 1-methylphenanthrene, m. p. and mixed m. p. 118° (picrate, m. p. and mixed m. p. 136°).

N-*Tetrahydrobenzoyl*-o-*nitroaniline*.—Tetrahydrobenzoic acid (1·7 g.), prepared by Dreiding and Hartman's method,[12] was warmed with an excess of thionyl chloride for 3 hr. after which

[10] Chuang, Tien, and Ma, *Ber.*, 1936, **69**, 1502.
[11] Kon and Thakur, *J.*, 1930, 2222.
[12] Dreiding and Hartman, *J. Amer. Chem. Soc.*, 1953, **75**, 942.

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the excess was removed under reduced pressure. Pyridine (5 ml.) was added to the well-cooled acid chloride, followed by *o*-nitroaniline (1·9 g.). The mixture was kept at room temperature for 1 hr., then heated on the steam-bath. Dilution with water precipitated N-*tetrahydrobenzoyl*-o-*nitroaniline* (2·3 g.), which crystallised from ethanol in yellow needles, m. p. 68° (Found: C, 63·2; H, 5·4. $C_{13}H_{14}O_3N_2$ requires C, 63·5; H, 5·7%).

N-*Tetrahydrobenzoyl*-N-*methyl*-o-*nitroaniline*.—The above anilide (4·2 g.) in acetone (40 ml.) and 20% aqueous sodium hydroxide (40 ml.) was boiled under reflux while dimethyl sulphate (8 ml.) was added dropwise. After 15 min. the solution was cooled and diluted with water. The yellow precipitate was collected. Recrystallisation from ethanol gave the N-*methyl derivative* (3·4 g.) in yellow cubes, m. p. 109° (Found: C, 64·7; H, 6·1. $C_{14}H_{16}O_3N_2$ requires C, 64·7; H, 6·1%).

N-*Tetrahydrobenzoyl*-N-*methyl*-o-*phenylenediamine*.—The above methyl-nitro-compound (0·2 g.) in methanol (100 ml.) was shaken with hydrogen at atmospheric pressure in the presence of 5% palladium–charcoal (0·2 g.) until the required volume of hydrogen had been absorbed. The resulting solution was filtered and evaporated to dryness under reduced pressure. Crystallisation of the residue from methanol gave N-*tetrahydrobenzoyl*-N-*methyl*-o-*phenylenediamine* (0·11 g.) in rhombic needles, m. p. 103° (Found: C, 73·4; H, 7·8. $C_{14}H_{18}ON_2$ requires C, 73·1; H, 7·8%). The aqueous diazonium chloride prepared from this base was treated with copper powder in the usual manner. The product was worked up as in the preceding examples but chromatography gave only gums and tars.

N-*Tetrahydrobenzoyl*-NN′-*di*cyclo*hexylurea* (cf. ref. 7).—A solution of tetrahydrobenzoic acid (0·8 g.) and *NN*′-*dicyclo*hexylcarbodi-imide (1·3 g.) in methylene dichloride (10 ml.) was kept at room temperature for 2 hr. Di*cyclo*hexylurea, m. p. 216° (0·4 g.), separated. Evaporation of the filtrate gave a gum, which on trituration with water afforded N-*tetrahydrobenzoyl*-NN′-*di*cyclo*hexylurea* (0·4 g.), which crystallised from acetone in needles, m. p. 160—161° (Found: C, 72·4; H, 9·8; N, 8·2. $C_{20}H_{32}O_2N_2$ requires C, 72·3; H, 9·6; N, 8·4%). A similar result was obtained when the reaction was carried out with the addition of *o*-nitroaniline (0·9 g.).

N-*Hexahydrobenzoyl*-N-*methyl*-o-*nitroaniline*.—(i) Dimethyl sulphate (9 ml.) was added dropwise to a boiling solution of *N*-hexahydrobenzoyl-*o*-nitroaniline [13] (10 g.) in a mixture of acetone (10 ml.) and 10% aqueous sodium hydroxide (50 ml.). After 10 minutes' boiling the mixture was poured into water. Crystallisation from dilute ethanol of the solid which separated gave N-*hexahydrobenzoyl*-N-*methyl*-o-*nitroaniline* (6·3 g.) in greenish-yellow needles, m. p. 113° (Found: C, 64·2; H, 6·7. $C_{14}H_{18}O_3N_2$ requires C, 64·2; H, 6·9%).

(ii) *cyclo*Hexanecarboxylic acid (4·8 g.) was boiled with thionyl chloride (10 ml.) for 1 hr., after which the excess of thionyl chloride was removed under reduced pressure with the aid of added dry benzene. A cold solution of *N*-methyl-*o*-nitroaniline (5·8 g.) in pyridine (10 ml.) was added to the crude acid chloride cooled in ice. After being left overnight, the mixture was heated on a boiling-water bath for 2 hr., then poured into water (100 ml.). Recrystallisation from dilute ethanol of the precipitated solid gave *N*-hexahydrobenzoyl-*N*-methyl-*o*-nitroaniline (4·3 g.) in greenish-yellow needles m. p. 113°, identical with the specimen prepared by method (i).

N-*Hexahydrobenzoyl*-N-*methyl*-o-*phenylenediamine*.—The above nitro-compound (1·6 g.) in methanol (100 ml.) containing 5% palladium–charcoal (0·2 g.) was shaken with hydrogen at atmospheric pressure until the required volume had been absorbed. After filtration the solvent was removed under reduced pressure. Trituration of the residual brown oil with light petroleum (b. p. 40—60°) gave N-*hexahydrobenzoyl*-N-*methyl*-o-*phenylenediamine* (0·85 g.), which crystallised from benzene–light petroleum (b. p. 40—60°) in needles, m. p. 93·5° (Found: C, 72·7; H, 8·5. $C_{14}H_{20}ON_2$ requires C, 72·6; H, 8·6%). When a stream of dry hydrogen chloride was passed into a solution of this base (2·0 g.) in dry ether (20 ml.) 2-cyclo*hexyl*-1-*methylbenzimidazole* (1·1 g.) separated in needles, m. p. 104° (Found: C, 78·6; H, 8·5. $C_{14}H_{18}N_2$ requires C, 78·4; H, 8·4%).

Decomposition of the Diazonium Chloride from N-*Hexahydrobenzoyl*-N-*methyl*-o-*phenylenediamine*.—The amine (7·7 g.), suspended in concentrated hydrochloric acid (20 ml.) and water (150 ml.), was diazotised at 0—5° with sodium nitrite (3·3 g.) in water (40 ml.). During the diazotisation ethanol (50 ml.) was added and stirring was continued for 3 hr., after which urea (3·5 g.) was added, followed by copper powder (2 g.). There was an immediate evolution of nitrogen. The mixture was stirred at room temperature overnight (negative reaction with alkaline β-naphthol), then worked up as in the previous case. The resulting red oil was chromatographed in 1 : 2 benzene–light petroleum (b. p. 40—60°) on alumina (90 g.). Elution with

[13] Herbst, Roberts, Givens, and Harvill, *J. Org. Chem.*, 1952, **17**, 262.

the same solvent (200 ml.) yielded a colourless gum (*A*) (1·8 g.) after which elution with a 1 : 1 mixture (300 ml.) gave *N-hexahydrobenzoyl-N-methylaniline* (0·8 g.), needles (from dilute methanol), m. p. 62·5° (Found: C, 77·1; H, 8·3. $C_{14}H_{18}ON$ requires C, 77·6; H, 8·3%), identical with a specimen prepared from *cyclo*hexanecarboxyl chloride and *N*-methylaniline in pyridine. Further elution with ether (350 and 200 ml.) and with alcohol (200 ml.) gave gums (0·2 g., 0·3 g., and 1·1 g. respectively). The infrared spectrum of fraction (*A*) indicated the presence of carbonyl (1715 cm.$^{-1}$) and amide (1668 cm.$^{-1}$) groups. This fraction was distilled at 87°/0·1 mm. and the distillate (1·3 g.) was again chromatographed in 1 : 2 benzene–light petroleum (b. p. 40—60°) on alumina. Elution with the same solvent (150, 50, and 50 ml.) gave gums (*a*—*c*) (0·1, 0·02, and 0·03 g. respectively). Further elution with the same solvent (100 ml.) gave a gum from which *N*-hexahydrobenzoyl-*N*-methylaniline (0·5 g.), m. p. 62·5°, separated. The infrared spectra of the first three fractions showed a strong band at 1715 cm.$^{-1}$ but the band at 1668 cm.$^{-1}$ was considerably diminished. Further chromatography of the fractions (*a*) and (*b*) gave a ketonic product, which showed strong absorption at 1715 and a weak band at 1650 cm.$^{-1}$ (Found: C, 76·3; H, 8·1; N, 5·85%). *N*-Hexahydrobenzoyl-*N*-methylaniline shows no absorption at 1715 cm.$^{-1}$ but strong bands at 1667 and 704 cm.$^{-1}$.

N-Methyl-2-oxocyclohexanecarboxyanilide.—2-Oxo*cyclo*hexanecarboxylic acid (1·1 g.), methylaniline (0·83 g.), and *NN'*-di*cyclo*hexylcarbodi-imide [7] (1·6 g.) were dissolved in methylene dichloride. *NN'*-Di*cyclo*hexylurea was immediately precipitated. After 2 hr. the solution was filtered and the filtrate was washed successively with N-hydrochloric acid, aqueous potassium hydrogen carbonate, and water. Removal of the solvent from the dried (Na_2SO_4) solution left an oil, which was adsorbed from benzene on alumina. Elution with benzene gave *N-methyl-2-oxocyclohexanecarboxyanilide* (0·8 g.), b. p. 115—120°/0·10—0·13 mm. (Found: C, 72·9; H, 8·0. $C_{14}H_{17}O_2N$ requires C, 72·8; H, 7·4%), having strong infrared absorption at 1715, 1668, 779, and 704 cm.$^{-1}$.

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446. *Syntheses from Phthalimido-Acids. Part X.* Derivatives of* DL-*Penicillamine.*

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In model experiments for a synthesis of the DL-penicillamine analogue (penithione) of glutathione, *S*-benzyl-DL-penicillaminylglycine ethyl ester was prepared *via* the phthaloyl derivative and converted into phthaloyl-γ-DL-glutamyl-*S*-benzyl-DL-penicillaminylglycine ethyl ester from which the amorphous *S*-benzylpenithione was obtained. Two other dipeptide derivatives, *viz.*, glycyl-*S*-benzyl-DL-penicillamine and phthaloyl-γ-DL-glutamyl-*S*-benzyl-DL-penicillamine, are also described.

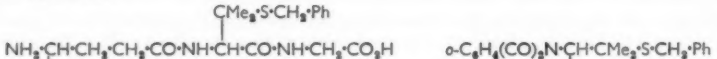
EXPLORATORY experiments with phthaloyl derivatives, similar to those having glutathione as their objective,* have been carried out with DL-penicillamine in a parallel investigation directed towards the synthesis of the penicillamine analogue of glutathione. The *S*-benzyl derivative (I) of γ-DL-glutamyl-DL-penicillaminylglycine was obtained in five steps from *S*-benzylpenicillamine (17% over-all), but the synthesis suffers from defects discussed earlier for that of glutathione,[1] and it was subsequently discontinued in favour of an examination of the thiazolidine route as described in the following paper.

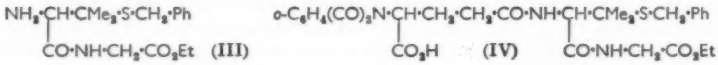
S-Benzyl-*N*-phthaloyl-DL-penicillamine (II; R = OH) was newly prepared and characterised as the methyl and ethyl esters (II; R = OMe or OEt). The acid chloride gave the amide and anilide (II; R = NH_2 or NHPh) with ammonia and aniline respectively, but

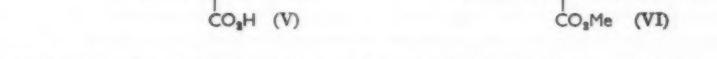
* Part IX, *J.*, 1957, 886.

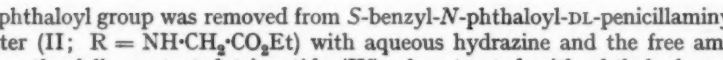
[1] King, Clark-Lewis, and Wade, *J.*, 1957, 880.

reacted with two molecules of the more basic benzylamine to give the bisbenzylamide of *S*-benzyl-*N*-*o*-carboxybenzoyl-DL-penicillamine in high yield. Under similar conditions, however, glycine ethyl ester gave the desired *S*-benzyl-*N*-phthaloyl-DL-penicillaminylglycine ethyl ester (II; R = NH·CH_2·CO_2Et) (65%), and the ester was hydrolysed to the protected dipeptide (II; R = NH·CH_2·CO_2H) by alkaline hydrolysis and subsequent treatment with acid.









The phthaloyl group was removed from *S*-benzyl-*N*-phthaloyl-DL-penicillaminylglycine ethyl ester (II; R = NH·CH_2·CO_2Et) with aqueous hydrazine and the free amino-ester (III) gave the fully protected tripeptide (IV) when treated with phthaloyl-DL-glutamic anhydride. Difficulty was experienced in stepwise removal of the protecting groups, but simultaneous removal of the ester and phthaloyl residues was achieved by the method of Grassmann and Schulte-Uebbing,[2] which gave the *S*-benzyl-tripeptide (*S*-benzylpenithione) in 73% yield as a deliquescent amorphous powder with the correct elementary composition. Debenzylation [3] of this product with sodium and liquid ammonia gave a thiol which was precipitated with mercuric sulphate reagent.[4] An attempt to prepare the cuprous derivative of the thiol by the method described [3] for glutathione gave a water-soluble copper derivative, which was isolated by addition of ethanol. Although this derivative contained the expected proportion of copper neither the composition of the remainder nor that of the regenerated thiol corresponded to the expected formula.

S-Benzyl-DL-penicillamine gave phthaloyl-γ-DL-glutamyl-*S*-benzyl-DL-penicillamine when treated with phthaloyl-DL-glutamic anhydride, and with phthaloylglycyl chloride gave phthaloylglycyl-*S*-benzyl-DL-pencillamine (95%) which was converted into glycyl-*S*-benzyl-DL-penicillamine by removal of the phthaloyl group with hydrazine.

The ready formation of *N*-phthaloyl-γ-glutamyl derivatives by interaction of phthaloylglutamic anhydride with bases or with alcohols has been demonstrated in previous parts of this series, and this property has already been utilised in a synthesis of glutathione,[1] the most important of the natural γ-glutamyl peptides. The value of the anhydride in the preparation of esters has been illustrated for γ-methyl hydrogen phthaloyl-L-glutamate (V) obtained directly from methanol, and for γ-methyl hydrogen phthaloyl-L-glutamate (VI) prepared indirectly from the γ-benzyl ester.[5] The γ-methyl ester (V) differs in m. p. from that described by Tipson [6] and although Tipson's α-methyl ester resembles our ester (VI) in m. p. and optical rotation, its infrared absorption (curve 7) is incompatible with the assigned structure; indeed the absorption near 3200 cm.$^{-1}$ indicates an amide and hence a phthalamic acid structure. Tipson's criticism of previous work [7] is thus probably ill-founded and his conclusions regarding the optical purity of Sheehan and Bolhofer's phthaloylglutamic anhydride overlook and merely confirm published results.[8]

[2] Grassmann and Schulte-Uebbing, *Chem. Ber.*, 1950, **83**, 244.
[3] du Vigneaud and Miller, *J. Biol. Chem.*, 1936, **116**, 469.
[4] Kendal, Mason, and McKenzie, *ibid.*, 1929, **84**, 669.
[5] King, Clark-Lewis, and Wade, *J.*, 1957, 886.
[6] Tipson, *J. Org. Chem.*, 1956, **21**, 1353.
[7] King and Kidd, *J.*, 1949, 3315.
[8] Clark-Lewis and Fruton, *J. Biol. Chem.*, 1954, **207**, 477.

Experimental

Racemic penicillamine was used throughout this work and the prefix DL has therefore been omitted below.

S-*Benzyl*-N-*phthaloylpenicillamine* (II; R = OH) *and its Methyl and Ethyl Ester.*—*S*-Benzylpenicillamine (10 g.), m. p. 199° (decomp.) [lit.,[9] m. p. 197—198° (decomp.)], prepared from *N*-acetylpenicillamine, was heated for 12 hr. with phthalic anhydride (12·4 g., 2 mol.) in boiling acetic acid (125 c.c.). The hot filtrate was diluted with boiling water until turbid and the product (10 g., 65%), m. p. 161—164°, was collected from the cold solution. Recrystallisation from aqueous ethanol or acetone gave S-*benzyl*-N-*phthaloylpenicillamine* in prisms, m. p. 164° (Found: C, 65·0; H, 5·5; N, 3·8. $C_{20}H_{19}O_4NS$ requires C, 65·0; H, 5·2; N, 3·8%). Diazomethane gave the *methyl ester*, prisms, m. p. 92° (from methanol) (Found: C, 65·7; H, 5·9; N, 3·9. $C_{21}H_{21}O_4NS$ requires C, 65·8; H, 5·5; N, 3·7%), and ethanolic hydrogen chloride at room temperature for 72 hr. gave the *ethyl ester* in plates (from ethanol), m. p. 103—104° (Found: C, 66·7; H, 5·4; N, 3·3. $C_{22}H_{23}O_4NS$ requires C, 66·5; H, 5·8; N, 3·5%).

S-*Benzyl*-N-*phthaloylpenicillaminyl Chloride, Anilide, and Amide.*—(a) *Acid chloride.* Phosphorus pentachloride (6 g., 1·06 mol.) was added to an ice-cold suspension of powdered *S*-benzyl-*N*-phthaloylpenicillamine (10 g., 1 mol.) in dry chloroform (40 c.c.) and the mixture was cooled in an ice–salt bath and shaken intermittently during 35—45 min. The yellow solution was filtered through glass wool, and the filtrate was evaporated under reduced pressure (bath-temp. 20—25°) and the viscous residue was washed by decantation with cold light petroleum (b. p. 40—60°; 2 × 10 c.c.) before dissolution in cold, dry chloroform (40 c.c.); the solution was stored in an ice–salt bath. The acid chloride was also prepared from the acid and thionyl chloride at room temperature, and with methanol gave the methyl ester, m. p. and mixed m. p. 92°.

(b) *Anilide* (II; R = NHPh). Aniline (0·6 c.c., an excess) in ether (6 c.c.) was added to a stirred solution of the acid chloride (from the acid, 1·9 g.) in cold chloroform (*ca.* 12 c.c.). Next day the solvent was removed and the residue was washed with dilute acid and water. S-*Benzyl*-N-*phthaloylpencillaminanilide* crystallised from acetone–ethanol in needles (0·93 g., 40%), m. p. 159° (Found: C, 70·4; H, 5·3; N, 6·1. $C_{26}H_{24}O_3N_2S$ requires C, 70·3; H, 5·4; N, 6·3%).

(c) *Amide* (II; R = NH_2). A chloroform (2 c.c.) solution of the acid chloride (from 0·25 g. of acid) was treated with anhydrous ethereal ammonia at 0°, and the mixture was kept at room temperature for several hours and filtered. Evaporation of the filtrate left a residue of S-*benzyl*-N-*phthaloylpenicillaminamide* which crystallised from ethanol–light petroleum in needles (0·174 g., 70%), m. p. 164° (Found: C, 64·9; H, 5·4; N, 7·5. $C_{20}H_{20}O_3N_2S$ requires C, 65·2; H, 5·5; N, 7·6%).

[S-*Benzyl*-N-(o-N-*benzylcarbamoylbenzoyl*)*penicillaminyl*]*benzylamine.*—Benzylamine (1·5 c.c.) in ether (3·5 c.c.) was added to the above acid chloride (from 1·5 g. of acid) in chloroform (10 c.c.) under conditions already described for the anilide. Recrystallisation of the neutral product from 90% ethanol gave rectangular plates of the *benzylamide*, m. p. 169° (Found: C, 72·2; H, 6·4; N, 7·7. $C_{34}H_{33}O_3N_3S$ requires C, 72·2; H, 6·2; N, 7·4%).

S-*Benzyl*-N-*phthaloylpenicillaminylglycine and Ethyl Ester* (II; R = $NH{\cdot}CH_2{\cdot}CO_2Et$).—A chloroform solution (40 c.c.) of the acid chloride, prepared as already described from *S*-benzyl-*N*-phthaloylpenicillamine (10 g.), was added slowly to a cooled and stirred solution of glycine ethyl ester (11 g., 4 mol.) in dry chloroform (60 c.c.). The mixture was kept at room temperature for several hours, diluted with dry ether, and filtered from glycine ethyl ester hydrochloride. The filtrate was washed with 0·1N-hydrochloric acid (2 × 100 c.c.) and water (2 × 50 c.c.), and the ethereal layer dried ($MgSO_4$) and evaporated. Crystallisation of the residue from ethanol–light petroleum (b. p. 60—80°) gave S-*benzyl*-N-*phthaloylpenicillaminylglycine ethyl ester* (8 g., 65%), m. p. 90—92° raised to 94—95° by recrystallisation from ethanol (Found: C, 63·7; H, 5·7; N, 6·2. $C_{24}H_{26}O_5N_2S$ requires C, 63·4; H, 5·8; N, 6·2%). 10N-Sodium hydroxide (1·5 c.c., 3·4 equiv.) was added to a solution of the ester (2 g.) in dry ethanol (40 c.c.) and when separation of the solid appeared to be complete (*ca.* 10 min.) the solvent was removed under reduced pressure. The residue was dissolved in water (15—20 c.c.) and acidified with concentrated hydrochloric acid, and the suspension then heated with sufficient ethanol to effect solution at the b. p. Crystallisation gave S-*benzyl*-N-*phthaloylpencillaminylglycine*

[9] "The Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 462.

sesquihydrate in rectangular plates (1·24 g., 62%), m. p. 178° after sintering at 118—120° (Found: C, 58·6; H, 5·7; N, 6·2. $C_{23}H_{22}O_5N_2S,1{\cdot}5H_2O$ requires C, 58·3; H, 5·6; N, 6·2%).

S-*Benzylpenicillaminylglycine Ethyl Ester Hydrochloride* (III).—32·8% Aqueous hydrazine (2·16 c.c.) was added to a solution of the ethyl phthaloyl ester (10 g.) described in the preceding paragraph in a mixture of dioxan (50 c.c.) and ethanol (50 c.c.). A granular precipitate was formed when the solution was kept at room temperature and, after 65 hr., the suspension was acidified (Congo Red) with hydrochloric acid and kept at 0° for 14 hr. before collection of phthalhydrazide. Evaporation of the filtrate (bath-temp. 35—40°) left a pale yellow viscous residue which was shaken with a mixture of aqueous sodium hydrogen carbonate and ether. The ethereal layer was dried ($MgSO_4$) and then saturated with dry hydrogen chloride, and the amino-ester hydrochloride (4·75 g., 60%), m. p. 106—110°, was collected after 3—4 hr. Recrystallisation of the product from ethanol–ether or from propan-2-ol–light petroleum (b. p. 60—80°) gave S-*benzylpenicillaminylglycine ethyl ester hydrochloride* in colourless needles, m. p. 110—111° (Found: C, 52·2, 51·9; H, 7·0, 7·3; N, 7·5. $C_{16}H_{25}O_3N_2ClS,\frac{1}{2}H_2O$ requires C, 52·0; H, 7·1; N, 7·6%. Found, on material dried at 80°: C, 53·8; H, 7·2; N, 7·5; loss on drying, 2·5. $C_{16}H_{25}O_3N_2ClS$ requires C, 53·3; H, 7·0; N, 7·8; loss 2·5%). The corresponding *dioxopiperazine* crystallised from aqueous acetone in needles, m. p. 233°, insoluble in dilute hydrochloric acid and in aqueous sodium hydrogen carbonate (Found: C, 60·8; H, 7·1. $C_{14}H_{16}O_2N_2S$ requires C, 60·4; H, 6·5%).

S-*Benzylpenicillaminylglycine.*—The foregoing ethyl ester and 0·3N-hydrochloric acid (10 c.c. per g.) were heated to the b. p. and the filtered solution was treated with sodium acetate. Insoluble material was digested with aqueous ethanol and collected next day; crystallisation from water gave S-*benzylpenicillaminylglycine* in plates, m. p. 233—234° (decomp.) (Found: C, 56·6; H, 6·8; N, 9·4. $C_{14}H_{20}O_3N_2S$ requires C, 56·7; H, 6·8; N, 9·5%). A solution of the dipeptide (0·45 g.) in 2N-hydrochloric acid (0·8 c.c.) evaporated to dryness when stored in a vacuum over sodium hydroxide; recrystallisation of the residue from ethanol–ether gave S-*benzylpenicillaminylglycine hydrochloride*, plates, m. p. 225—226° (Found: C, 50·3; H, 6·3; N, 8·3. $C_{14}H_{20}O_3N_2S,HCl$ requires C, 50·5; H, 6·4; N, 8·4%).

DL-*Phthaloyl-γ-glutamyl-S-benzylpenicillaminylglycine and Ethyl Ester* (IV).—A solution of *S*-benzylpenicillaminylglycine ethyl ester hydrochloride (5 g.) and anhydrous sodium acetate (1·2 g., 1·06 equiv.) in glacial acetic acid (28 c.c.) was heated with DL-phthaloylglutamic anhydride (3·59 g., 1 equiv.) on a steam-bath for 10 min. and then kept at room temperature for 20 min., filtered, and evaporated under reduced pressure. The residue was shaken with aqueous sodium hydrogen carbonate and ether containing a little chloroform, and the aqueous layer was filtered through kieselguhr into stirred 5N-hydrochloric acid (25 c.c.), and the precipitate (7·3 g., 90%) was collected, washed with a little cold water, and dried over phosphoric oxide. DL-*Phthaloyl-γ-glutamyl-S-benzylpenicillaminylglycine ethyl ester hydrate* crystallised from ethanol in plates, m. p. 126° after softening at 118° (Found: C, 57·3; H, 5·9; N, 6·7. $C_{29}H_{33}O_8N_3S,1{\cdot}5H_2O$ requires C, 57·1; H, 5·9; N, 6·9%). The *α-methyl ester*, prepared with diazomethane, crystallised from methanol in needles, m. p. 166° (Found: C, 60·6; H, 6·3; N, 7·1. $C_{30}H_{35}O_8N_3S$ requires C, 60·3; H, 5·9; N, 7·0%). Aqueous 10N-sodium hydroxide was added gradually to a solution of the ethyl ester (1·1 g.) in ethanol (11 c.c.) until the first permanent blue colour was obtained with thymolphthalein as indicator. Addition of one further equivalent of 10N-sodium hydroxide (0·58 c.c.) precipitated a sodium salt which, after evaporation of the solution to dryness, was dissolved in water. The filtered solution was then acidified with 0·5N-hydrochloric acid (10 c.c.). DL-*Phthaloyl-γ-glutamyl-S-benzylpenicillaminylglycine* (0·2 g., 20%) crystallised from aqueous dioxan, or from ethanol containing a little dioxan, in needles, m. p. 230—232° (Found: C, 58·5; H, 5·2; N, 8·0. $C_{27}H_{29}O_8N_3S$ requires C, 58·4; H, 5·3; N, 7·6%). The phthaloyltripeptide (0·12 g., 14%) was also obtained by direct coupling of *S*-benzylpenicillaminylglycine hydrochloride and phthaloyl-DL-glutamic anhydride in acetic acid containing sodium acetate (1 mol.).

γ-DL-*Glutamyl-S-benzylpenicillaminylglycine* (I).—Hydrated phthaloyl-γ-DL-glutamyl-*S*-benzylpenicillaminylglycine ethyl ester (3·05 g.) in alcoholic 0·87N-potassium hydroxide (11·5 c.c.) was heated with 32·8% aqueous hydrazine hydrate [2] (1·24 g.) under reflux for 2 hr. and the solution was then evaporated under reduced pressure. A solution of the residue in water (25 c.c.) was adjusted to pH 6·0 with acetic acid, heated on a steam-bath for 1 hr., and then filtered from phthalhydrazide. Evaporation of the filtrate at 35—40° left a viscous solution which gave γ-DL-*glutamyl-S-benzylpenicillaminylglycine* (1·55 g., 73%) when diluted with

ethanol. The deliquescent amorphous tripeptide was reprecipitated from moist alcoholic solution by addition of dry ethanol, and it melted in a sealed capillary at 172—173° after sintering at 116° (Found: C, 53·6; H, 6·4; N, 9·8. $C_{19}H_{27}O_6N_3S$ requires C, 53·6; H, 6·4; N, 9·9%). Debenzylation of the tripeptide (0·88 g.) with sodium in liquid ammonia gave a product isolated as the mercury derivative (1·58 g.),[4] which was freed from mercury with hydrogen sulphide and then converted with cuprous oxide into an unidentified copper derivative (0·33 g.). This was precipitated as a pale green powder, m. p. 194° (decomp.), by addition of ethanol (Found: C, 24·4; H, 4·9; N, 7·7; S, 9·0; Cu, 16·0%). Removal of copper as the sulphide gave an amorphous product of indefinite m. p., *ca.* 178°, which failed to crystallise on slow evaporation of an aqueous-ethanolic solution (Found: C, 32·1, 32·7; H, 5·6, 5·6; N, 12·6%).

*Phthaloyl-γ-*DL*-glutamyl-*S*-benzylpenicillamine.*—A mixture of *S*-benzylpenicillamine (1 g.) and phthaloyl-DL-glutamic anhydride (1·08 g., 1 mol.) in dry dioxan (20 c.c.) was boiled for 20 min., filtered, and evaporated under reduced pressure. The residue separated from aqueous dioxan as a colourless solid (0·4 g., 19%), m. p. 130—132°, and recrystallisation from aqueous alcohol gave *phthaloyl-γ-*DL*-glutamyl-*S*-benzylpenicillamine dihydrate* in rectangular plates, m. p. 130—132° (decomp.) (Found: C, 56·1; H, 5·8; N, 5·3. $C_{25}H_{26}O_7N_3S,2H_2O$ requires C, 56·2; H, 5·7; N, 5·2%).

*Phthaloylglycyl-*S*-benzylpenicillamine.*—Phthaloylglycyl chloride (4 g., 1 mol.) in glacial acetic acid (20 c.c.) was added during 20 min. to a stirred solution of *S*-benzylpenicillamine (8·52 g., 2 mol.) in acetic acid (120 c.c.). The solution was stirred for 2 hr. and kept at room temperature for 4 hr. before evaporation under reduced pressure (bath-temp. 45°). The residue was treated with 2N-hydrochloric acid, and insoluble material crystallised from aqueous ethanol (7·19 g., 95%; m. p. 177—180°). Recrystallisation from ethanol–light petroleum gave *phthaloylglycyl-*S*-benzylpenicillamine* in hard prisms, m. p. 183° (Found: C, 62·0; H, 5·2; N, 6·9. $C_{22}H_{23}O_5N_3S$ requires C, 61·9; H, 5·2; N, 6·6%). *S*-Benzylpenicillamine (*ca.* 2 g.) was recovered by adding an excess of sodium acetate to the acid solution.

*Glycyl-*S*-benzylpenicillamine.*—The preceding phthaloyl compound (3 g., 1 mol.) was heated on a steam-bath under reflux with alcoholic 0·33N-potassium hydroxide (21 c.c., 1 equiv.) and 50% aqueous hydrazine hydrate (0·7 g., 1 equiv.). The solution soon became turbid and after 40 min. further ethanol (7 c.c.) was added and heating was continued for a total of 2 hr. before filtration. The solid residue (3·1 g.) and the filtrate were heated separately with 0·6N-hydrochloric acid (50 c.c.) at 50° for 5 min., and filtered when cold from phthalhydrazide. The combined filtrates were partially neutralised with sodium hydroxide before addition of saturated aqueous sodium acetate to precipitate the product which was collected and washed with hot ethanol (10—15 c.c.). *Glycyl-*S*-benzylpenicillamine* (1·68 g., 80%) crystallised in rectangular plates, m. p. 228° raised to 231° by recrystallisation from water (Found: C, 56·7; H, 6·8; N, 9·6. $C_{14}H_{20}O_3N_2S$ requires C, 56·7; H, 6·8; N, 9·5%).

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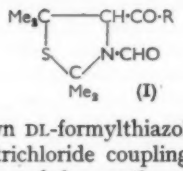
UNIVERSITY OF NOTTINGHAM. [*Received, February 2nd,* 1959.]

447. *Thiazolidines in the Synthesis of Penicillamine Peptides.*

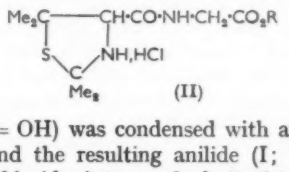
By F. E. King, J. W. Clark-Lewis, G. R. Smith, and Roy Wade.

DL-3-Formyl-2 : 2 : 5 : 5-tetramethylthiazolidine-4-carboxylic acid, when coupled by the Süs method with aniline and with glycine methyl and ethyl esters, gave products isolated as the thiazolidine hydrochlorides. The D-acid was converted by mixed anhydride coupling and subsequent deformylation into D-4-*N*-methoxycarbonylmethylcarbamoyl-2 : 2 : 5 : 5-tetramethylthiazolidine hydrochloride, an intermediate applicable to the synthesis of a D-penicillamine analogue of glutathione.

Thiazolidinecarboxylic acids are useful for the synthesis of peptides from α-amino-β-mercapto-acids, as illustrated recently for glutathione.[1] These thiazolidines [2] may be prepared by interaction of amino-mercapto-acids and either aldehydes or ketones, but only the *iso*propylidene derivatives of cysteine [1,3,4] and penicillamine [3] have so far been applied to peptide synthesis. Unsuccessful attempts to couple [5] the thiazoline derived from *N*-acetyl-DL-penicillamine led us to investigate thiazolidine derivatives of penicillamine as intermediates in peptide synthesis instead of the thiazolines, thereby eliminating also the reduction stage entailed with thiazolines.



(I)



(II)

The known DL-formylthiazolidine [6] (I; R = OH) was condensed with aniline by the phosphorus trichloride coupling procedure [7] and the resulting anilide (I; R = NHPh) readily converted by methanolic hydrogen chloride into DL-2 : 2 : 5 : 5-tetramethyl-4-phenylcarbamoylthiazolidine hydrochloride. Similar condensation of the acid (I; R = OH) with glycine ethyl and methyl esters, followed by alcoholysis of the intermediate formyl compounds, gave the thiazolidine dipeptide hydrochlorides (II; R = Et and Me). The methyl ester hydrochloride (II; R = Me) prepared in this way [8] has also been obtained by interaction of DL-penicillaminylglycine methyl ester hydrochloride and acetone.[9]

The phosphorus trichloride coupling procedure caused racemisation [1] of the formylthiazolidinecarboxylic acid derived from L-cysteine, and was therefore avoided in preparing D-penicillamine derivatives. Preparation of D-3-formyl-4-*N*-methoxycarbonylmethylcarbamoyl-2 : 2 : 5 : 5-tetramethylthiazolidine (I; R = NH·CH_2·CO_2Me) was achieved instead by mixed anhydride coupling of the D-acid (I; R = OH) with glycine methyl ester as already described for the L-cysteine analogue.[1] The product was found to be dimorphic (m. p.s 88—89° and 120—121°) and was obtained initially in the less stable, lower-melting form. Removal of the formyl group with methanolic hydrogen chloride then gave the D-dipeptide ester hydrochloride (II; R = Me) in which the thiol grouping is still masked and the amine function is exposed for further coupling to a tripeptide derivative, *e.g.*, by reaction with phthaloylglutamic anhydride as for the cysteine analogue.[1]

The compounds illustrate further the value of thiazolidine intermediates [1,4] in the synthesis of α-amino-β-mercapto-acid derivatives. The formyl group is readily removed

[1] King, Clark-Lewis, and Wade, *J.*, 1957, 880.
[2] Cook and Heilbron in "The Chemistry of Penicillin," Princeton Univ. Press, Princeton, 1949, p. 921.
[3] Sheehan and Armstrong, 122nd Meeting Amer. Chem. Soc., 1952, Abs. No. 23, p. 15M.
[4] Sheehan and Yang, *J. Amer. Chem. Soc.*, 1958, **80**, 1158.
[5] Swindin, Thesis, Nottingham, 1953.
[6] "The Chemistry of Penicillin," Princeton Univ. Press, Princeton, 1949, p. 960.
[7] Süs and Hoffman, *Annalen*, 1951, **572**, 96.
[8] Smith, Thesis, Nottingham, 1953.
[9] Heilbron and Cook, B.P. 681,900/1952; *Chem. Abs.*, 1954, **48**, 735.

with alcoholic hydrogen chloride which leaves the thiazolidine ring intact, and the latter may then be opened with mercuric chloride; subsequent treatment with hydrogen sulphide then liberates the thiol function. Some of the compounds described here formed the subject of a preliminary announcement by Sheehan and Armstrong.[3]

Experimental

DL-3-*Formyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylic Acid*.—*N*-Acetyl-DL-penicillamine (10 g.) in 1·07N-hydrochloric acid (160 c.c.) was boiled under nitrogen for 16 hr. before evaporation under reduced pressure (nitrogen), and the residue was dried azeotropically. The penicillamine hydrochloride crystallised when triturated with anhydrous ether, and when boiled with acetone (100 c.c.) it gave 2 : 2 : 5 : 5-tetramethylthiazolidine-4-carboxylic acid hydrochloride (9·45 g.; 80%), m. p. 199° (decomp.). The hydrochloride (7·5 g.) was stirred with 98% formic acid (35 c.c.) and sodium formate (2·5 g.) at 20° during addition in 1 hr. of acetic anhydride (15 g.). Next day water (15 c.c.) was added and the solution was evaporated to dryness under reduced pressure; recrystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave DL-3-formyl-2 : 2 : 5 : 5-tetramethylthiazolidine-4-carboxylic acid (6·8 g.; 94%) in colourless plates, m. p. 141° (lit.,[6] m. p. 141—142°).

DL-3-*Formyl*-2 : 2 : 5 : 5-*tetramethyl*-4-*phenylcarbamoylthiazolidine*.—Phosphorus trichloride (0·9 c.c.) was added to the above formyl compound (1·9 g.) and aniline (1·5 c.c.) in dry benzene (50 c.c.), and the mixture was boiled under reflux for 5 hr. before being evaporated to dryness under reduced pressure. The residue insoluble in aqueous sodium carbonate consisted of DL-3-*formyl*-2 : 2 : 5 : 5-*tetramethyl*-4-*phenylcarbamoylthiazolidine* which crystallised from aqueous ethanol (charcoal) in prisms, m. p. 178—179° raised to 182° by recrystallisation (Found: C, 62·0; H, 6·6; N, 9·3. $C_{15}H_{20}O_2N_2S$ requires C, 61·6; H, 6·9; N, 9·6%).

DL-2 : 2 : 5 : 5-*Tetramethyl*-4-*phenylcarbamoylthiazolidine Hydrochloride*.—The foregoing anilide (0·21 g.) was boiled for 5 min. with anhydrous methanol (25 c.c.) containing dry hydrogen chloride (2%), and the solution then stored at room temperature. Next day the solution was evaporated under reduced pressure and the residue, when triturated with dry ether, gave DL-2 : 2 : 5 : 5-*tetramethyl*-4-*phenylcarbamoylthiazolidine hydrochloride* (0·12 g.; 56%), m. p. 206—208° (decomp.), which crystallised from methanol–ether in prisms, m. p. 212° (decomp.) (Found: C, 56·1; H, 6·9; N, 9·5. $C_{14}H_{20}ON_2S,HCl$ requires C, 55·9; H, 7·0; N, 9·3%).

DL-4-N-*Ethoxycarbonylmethylcarbamoyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine Hydrochloride*.—A mixture of DL-3-formyl-2 : 2 : 5 : 5-tetramethylthiazolidine-4-carboxylic acid (1·9 g.), freshly distilled glycine ethyl ester (1·7 g.), dry benzene (50 c.c.), and phosphorus trichloride (0·9 g.) was heated in a steam-bath for 5 hr. Evaporation of the solution left a residue which was dissolved in ether, and the solution was washed with aqueous sodium carbonate and dried ($MgSO_4$) before evaporation under reduced pressure. The residue was boiled with 1·5% ethanolic hydrogen chloride (25 c.c.) for 5 min., then kept for 14 hr. before evaporation under reduced pressure. Recrystallisation of the residue from dry methanol–ether gave DL-4-N-*ethoxycarbonylmethylcarbamoyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine hydrochloride* in needles, m. p. 200° (decomp.) (Found: C, 46·6; H, 7·3; N, 8·9. $C_{12}H_{22}O_3N_2S,HCl$ requires C, 46·4; H, 7·5; N, 9·0%).

DL-4-N-*Methoxycarbonylmethylcarbamoyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine Hydrochloride*.—The formyl compound (1·9 g.) and freshly distilled glycine methyl ester (1·7 g.) were treated with phosphorus trichloride in benzene as described above for the ethyl ester, and the neutral formyl ester was precipitated from benzene with light petroleum (b. p. 60—80°). Removal of the formyl group with dry methanolic hydrogen chloride gave DL-4-*N*-methoxycarbonylmethylcarbamoyl-2 : 2 : 5 : 5-tetramethylthiazolidine hydrochloride (0·97 g.; 38%), which crystallised from dry methanol–ether in prisms, m. p. 219—220° (decomp.) (lit.,[3] m. p. 225—227°) (Found: C, 44·7; H, 7·0; N, 9·1. Calc. for $C_{11}H_{20}O_3N_2S,HCl$: C, 44·5; H, 7·1; N, 9·4%).

D-3-*Formyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylic Acid*.—Crude potassium benzylpenicillin was hydrolysed in batches of 1 g. or 2 g. with 0·1N-sulphuric acid (or hydrochloric acid), and the D-penicillamine, isolated as the mercury derivative, was converted by acetone into the thiazolidine hydrochloride, m. p. 198° (decomp.). The hydrochloride was converted by formylation as described above for the racemic compound into D-3-formyl-2 : 2 : 5 : 5-thiazolidine-4-carboxylic acid (5·18 g.; 13% from the crude potassium benzylpenicillin, 67 g.),

m. p. 180—181°, $[\alpha]_D^{20}$ +53·7° (1% in EtOH) (lit.,[10] m. p. 179—180°, $[\alpha]_D$ +54°) (Found: C, 49·5; H, 6·9; N, 6·4. Calc. for $C_9H_{15}O_3NS$: C, 49·7; H, 7·0; N, 6·4%).

D-3-*Formyl*-4-N-*methoxycarbonylmethylcarbamoyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine*.—The formylthiazolidinecarboxylic acid (5·2 g.) in dry chloroform (60 c.c.) was treated at 0° with triethylamine (3·32 c.c.) and *iso*butyl chloroformate (3·14 c.c.), and after 10 min. a suspension of finely powdered glycine methyl ester hydrochloride (3·3 g.; 1·1 mol.) and triethylamine (3·65 c.c.; 1·1 mol.) in dry chloroform (30 c.c.) was added. Next day the solution was washed with water, aqueous sodium hydrogen carbonate, and water, and dried ($MgSO_4$) before removal of the chloroform under reduced pressure. The residue of D-3-*formyl*-4-N-*methoxycarbonylmethylcarbamoyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine* crystallised from ethyl acetate–light petroleum in prisms (2·74 g.; 40%), m. p. 88—89°, $[\alpha]_D^{21}$ +52·9° (0·5% in $CHCl_3$) (Found: C, 50·1; H, 7·1; N, 9·6. $C_{12}H_{20}O_4N_2S$ requires C, 50·0; H, 7·0; N, 9·7%). The dipeptide derivative was dimorphic, the more stable form having m. p. 120—121° (alone or when mixed with the material of m. p. 88—89°) and $[\alpha]_D^{23}$ +52·4° (0·5% in $CHCl_3$) (Found: C, 50·7; H, 7·1; N, 10·2%). Recrystallisation of the compound of m. p. 88—89° from ethyl acetate–hexane and seeding with the higher-melting form gave the dipeptide derivative in elongated prisms, m. p. 120—121°.

D-4-N-*Methoxycarbonylmethylcarbamoyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine Hydrochloride*.—The above formyl dipeptide ester (2 g.) was boiled for 5 min. with dry (Mg) methanol (60 c.c.) containing hydrogen chloride (1·5%), and the solution was cooled and evaporated under reduced pressure below 30° (bath). The residue crystallised when stored overnight in a vacuum over sulphuric acid and sodium hydroxide. Recrystallisation from methanol–ether (sodium-dried) gave the *thiazolidine hydrochloride* (1·56 g.; 76%) in prisms, m. p. 189—191° (decomp.), $[\alpha]_D^{26}$ +49·5° (0·5% in MeOH), which effloresced in a vacuum over sulphuric acid (Found, on dried material: C, 44·0; H, 7·3; N, 9·0. $C_{11}H_{20}O_3N_2S,HCl$ requires C, 44·5; H, 7·1; N, 9·4%).

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[10] " The Chemistry of Penicillin," Princeton Univ. Press, Princeton, 1949, p. 468.

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448. *Methylenebisphosphonates and Related Compounds. Part I. Synthesis from Methylene Halides.*

By J. A. CADE.

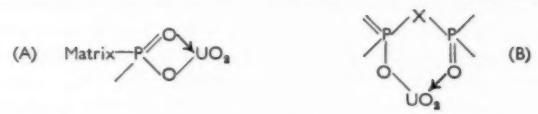
Two established methods for preparing ethyl methylenebisphosphonates can be extended to allyl systems, but with limited success. Only one method gave a product suitable for the preparation of resins for complex formation with metals. The yield of saturated alkyl esters has been improved, and some new esters containing phosphorus are described.

INTEREST in compounds containing a P–C–P bridge has hitherto been small, but the possibility that such compounds could form complexes with metals initiated a search for new methods of obtaining them.

Organic phosphates and phosphonates,[1] in resin form, take up uranium selectively from solutions containing a few mg. per l. Adsorption is considered to involve a chelate complex (A). From analogy with the very stable uranyl pyrophosphate complex, for which a six-membered ring structure has been suggested,[2] it was considered [3] that diphosphonic acids $X(PO_3H_2)_2$ might give uranyl complexes (B) of enhanced stability.

[1] Kennedy, *Chem. and Ind.*, 1956, 378; Kennedy and Davies, *Chem. and Ind.*, 1956, 378; A.E.R.E. Reports C/R 2329, C/R 2330, and unpublished work.
[2] Voegtlin and Hodge, " Pharmacology and Toxicology of Uranium Compounds," McGraw-Hill Co., New York, Vol. I, 1949.
[3] Kennedy and Lane, personal discussion.

Compounds of this type in which X = O, N, S, Sn, or C are known, but for durability of the resin it was desirable to have a carbon bridge, since in the other compounds hydrolysis affects the essential P–X–P bonds. This paper deals with application of the Michaelis–Becker and the Arbusov–Michaelis reaction [4] to give esters $CH_2(PO_3R'_2)_2$ (R = allyl, to



preserve continuity [1]). Yields were small, with formation of large amounts of undistillable residues and hazard of explosion during prolonged heating or at high temperatures, all due to a tendency for spontaneous polymerisation. The allyl esters, once isolated, could be redistilled with high recovery (>90%). The addition of a small quantity of quinol increased the yields of monomer.

Sodium Diallyl Phosphite and Methylene Dihalide.—Nylen [5] showed that the main product (40% yield) from methylene di-iodide and sodium diethyl phosphite was symmetrical disodium diethyl methylenebisphosphonate (I), believed to be due to reaction of the dialkyl phosphite in the " enol " form:

$$2(EtO)_2P{:}^{\diagup ONa} + CH_2I_2 \longrightarrow CH_2[P^+(OEt)_2{\cdot}ONa]_2\ 2I^- \longrightarrow CH_2[P(O)(OEt){\cdot}ONa]_2\ (I) + 2EtI$$

Sodium iodide, ethyl iodide, diethyl ethylphosphonate, and unchanged reactants were identified among the products but the required tetraethyl methylenebisphosphonate was not obtained. A reaction not involving elimination of alkyl groups could only be realised when a dihalide was used in which the halogen atoms are separated by at least three carbon atoms.

These observations have been corroborated by those for allyl systems. Methylene di-iodide or di-bromide with sodium diallyl phosphite gave allyl iodide, diallyl allylphosphonate, and disodium diallyl methylenebisphosphonate. It is unlikely that dealkylation occurs as depicted by Nylen. Neutral bisphosphonate is probably first formed, then dealkylated by halide ions, apparently with the aid of electron-delocalising substituents on the carbon atom attached directly to phosphorus in phosphonic acids.[6]

Attempts, by various techniques, to exclude moisture and free alcohol, and thus to prevent elimination of two alkyl residues, failed to give tetra-allyl methylenebisphosphonate.

Direct reaction of sodium with diallyl hydrogen phosphite in benzene or toluene was unsatisfactory for the preparation of sodium diallyl phosphite because a gel was deposited before all the sodium had dissolved. Addition of diallyl hydrogen phosphite to sodium allyloxide, followed by removal of allyl alcohol by repeated distillation with toluene, gave a very reactive product. When methylene dibromide was added to this, sodium bromide was precipitated immediately, but the reaction became uncontrollable after ¼ to ⅓ of an equivalent of methylene dibromide had been added, even at 0°. (Similar results were obtained with the chloride.) This could be prevented by addition of quinol, but reactivity was thus reduced and sodium bromide (equivalent in some experiments to 60—75% of the bromine in the system) was produced only after warming to 60° for some hours. In all experiments allyl bromide was produced, the main product being a viscous residue which could not be distilled or crystallised, but which in some cases contained derivatives of methylenebisphosphonic acid.

[4] See Kosolapoff, " Organophosphorus Compounds," Wiley, New York, 1950, pp. 121, 123.
[5] Nylen, Diss., Uppsala, 1930, pp. 77—84.
[6] Cf., *e.g.*, the preparation of ethyl aryloxymethylphosphonic acid from sodium aryloxide and diethyl iodomethylphosphonate; McGuire and Shaw, *Chem. and Ind.*, 1953, 668; *J.*, 1955, 1756.

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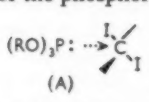
Attempts to obtain resins from some of these residues failed because the degree of polymerisation obtainable was insufficient to make them insoluble in water.

Trialkyl Phosphite and Methylene Dihalide.—There is controversy about application of the Arbusov–Michaelis reaction to methylene dihalides.

Arbusov and Kushkova [7] isolated only the monosubstitution product $(EtO)_2PO{\cdot}CH_2I$ from methylene di-iodide and triethyl phosphite, failed to obtain the tetraester bisphosphonate therefrom by use of sodium diethyl phosphite, but claimed that diethyl iodomethylphosphonate with potassium diethyl phosphite in 90% ethanol gave diethyl hydroxymethylphosphonate, which was the sole product from methylene di-iodide and potassium diethyl phosphite in ether. In contrast, Ford-Moore and Williams [8] obtained the bisphosphonate on using the di-iodide, though some halogenomethylphosphonate was also formed. Kosolapoff [9] found that when a 50% excess of phosphite is used the yield approaches 30%.

The reactivity of alkyl halides in this reaction is in the order $RI > RBr \gg RCl$, and decreases with increase in molecular weight. With methylene di-iodide, the by-product alkyl halide was produced in a one-phase reaction.[10] When trialkyl phosphite and an alkyl halide of sufficiently high boiling point were heated together, a temperature was attained at which reaction became self-ustaining. This temperature differed sufficiently among various halides used to be regarded as an approximate measure of the reactivity, which was found to be in the order $(EtO)_2PO{\cdot}CH_2Cl \ll (EtO)_2PO{\cdot}CH_2Br \sim (EtO)_2PO{\cdot}CH_2I < EtI > C_3H_5I \gg CH_2I_2$, with respect to triethyl or triallyl phosphite.

Gerrard and Green [11] have provided evidence that the reaction normally proceeds by two successive S_N2 steps. The low reactivity of methylene dihalide may therefore be attributed partly to impedance by the negative iodine atom to the in-line end-on approach of the phosphorus, necessitating a direction of attack requiring higher energy of activation (cf. A), and partly to the higher energy required to break the halogen–carbon bond when the latter atom is adjacent to another electron-withdrawing atom or group. The halogenomethylphosphonates are even less reactive, probably because of steric hinderance offered by the $(RO)_2P(O)-$ group, in addition to the foregoing factors.



(A)

The low reactivity of these halides makes the unwanted isomerisation more likely when the reactants are mixed before heating, especially as the formation of low-boiling alkyl halide tends to prevent the threshold temperature for fast reaction in the main sequence being attained. The importance of removing the more reactive by-product halide as it is formed has been recognised by previous investigators,[8] including Kabachnik and Medved [12] who attempted to blow it out with air. The isomerisation can also be further controlled by adding the trialkyl phosphite to the inactive halide held at a high temperature, at a slower rate than that at which the simple active halide is removed. Thus when diethyl iodomethylphosphonate and an excess of triethyl phosphite were merely heated together, nearly 90% of the latter reappeared as isomer. If however the phosphite was added slowly to the phosphonate at *ca.* 200° so that the instantaneous concentrations of both ethyl iodide and phosphite were kept to a minimum, almost 60% conversion into bisphosphonate was achieved. By using an excess of hot methylene di-iodide (the excess could be recovered), the yield of iodomethylphosphonate itself was improved to 90% with respect to the triethyl phosphite used, by the same technique. This represents a three-fold increase in the efficiency of the preparation of the bisphosphonate. The two stages could not, however, be combined, for although there was an overall reduction in the amount of diethyl ethylphosphonate formed, its accumulation necessitated prolonging the addition

[7] Arbusov and Kushkova, *J. Gen. Chem.* (*U.S.S.R.*), 1936, **6**, 283; *Chem. Abs.*, 1936, **30**, 4813.
[8] Ford-Moore and Williams, *J.*, 1947, 1465.
[9] Kosolapoff, *J.*, 1955, 3092.
[10] Contrast Kosolapoff, *J. Amer. Chem. Soc.*, 1944, **66**, 1511.
[11] Gerrard and Green, *J.*, 1951, 2550.
[12] Kabachnik and Medved, *Isvest. Akad. Nauk S.S.S.R.*, 1950, 635; *Chem. Abs.*, 1951, **45**, 8444.

in order to keep up the temperature and so led to a considerable undistillable residue. Apparently more bisphosphonate was formed, but the amount isolated was again only about 30%. Diethyl bromomethylphosphonate was nearly as reactive as the iodo-ester; an advantage in using the former was that it could be prepared from bromomethylphosphonyl dibromide, without the use of triethyl phosphite. Diethyl chloromethylphosphonate was ineffective.

The modified method had very limited success with allyl esters, because the prolonged

TABLE 1.

No.	Compound	Yield (%)	B. p./mm.	n_D	d_4
1	Triallyl phosphite [a]	90—92	34°/0·06	1·4589	0·999
2	Diallyl phosphite [b]	70—76	40°/0·07	1·4478	1·087
3	Diallyl allylphosphonate [c]	82	54°/0·08, 72°/0·45	1·4622	1·046
4	Diallyl chloromethylphosphonate [d]	60	83°/0·15	1·4665	1·175
5	Diallyl bromomethylphosphonate [d]	72	76°/0·1	1·4842	1·373
6	Diallyl iodomethylphosphonate	8; 41 [e]	102°/0·1	1·5015	1·552
7	Tetra-allyl methylenebisphosphonate	12	142°/0·1	1·4675	1·132
8	Diethyl bromomethylphosphonate [d]	82	121°/15, 56°/0·25	1·4595	1·432
9	Tetrabutyl methylenebisphosphonate [f]	45	150—155°/5 × 10^{-4} *	1·4455 †	1·041 †
10	Tetrabutyl ethylenebisphosphonate [f]	51	175—178°/5 × 10^{-4} *	1·4484, 1·4465 †	1·035

* Surface temperature during molecular distillation. † At 25°. Other values at 20°.

[a] Prepared by Ford-Moore and Williams's method.[6] [b] Toy and Cooper [17] give alternative physical constants; this ester was prepared by Gerrard's procedure [16] but at 25°. [c] From triallyl phosphite and excess of allyl iodide. An excess of the (low-boiling) iodide was used to avoid rise in temperature and possible violent decomposition. The ester was described by Kamai and Kukhtin [18] but the physical constants given by them (n_D^{20} 1·4600; d_4^{20} 1·005) lead to $[R_L]_D$ 55·1 (cf. Table 2). [d] Halogenomethylphosphonyl dichloride (1 equiv.) was added at −10° to sodium alkoxide (2 equiv.) prepared in excess of alcohol. Next morning the mixture was poured on ice and the oil which separated was extracted with methylene dichloride and worked up in the usual way. [e] Yields from Arbusov and Kushkova's method,[7] and the modification described in the Experimental section. [f] Prepared by the two-stage method used to obtain the tetraethyl ester as described in the Experimental section. The intermediate bromo-compounds were not purified. *Esters* 4—10 are new.

TABLE 2.

	Required (%)				Found (%)			
No.	C	H	P	$[R_L]_D$	C	H	P	$[R_L]_D$
1	53·5	7·5	15·3	55·33	53·6	7·4	15·3	55·32
2	44·5	6·85	19·1	39·32	45·25	7·05	19·2	39·17
3	53·5	7·5	15·3	53·33	52·95	7·4	15·3	53·17
4	39·9	5·75	14·7	49·3	39·9	5·75	14·2	49·66
5	33·0	4·7	12·15	52·2	32·95	4·8	12·4	53·16
6	27·85	4·0	10·25	57·41			10·4	57·4
7	46·4	6·6	18·4	82·26	46·65	6·8	18·1	82·5
8	26·0	5·2	13·4	43·76	25·9	5·4	13·35	44·16
9	51·0	9·6	15·5	102·54	50·85	9·6	16·1	102·54
10 *	52·2	9·4	14·95	107·19	50·35, 50·3	9·6, 9·6	14·4	107·25

* This ester is hygroscopic (cf. tetra*iso*propyl ethylenebisphosphonate [7]). Physical constants were determined in a dry-box, but weighings for the analyses were made in air; so the analytical results are low.

heating produced much residue. Adding triallyl phosphite to hot methylene di-iodide in excess gave diallyl iodomethylphosphonate in 41% yield, but the latter with triallyl phosphite above 190° gave unidentified unsaturated material boiling at 38°, and at higher temperatures violent decomposition was common. An optimum yield of only 12% of tetra-allyl methylenebisphosphonate was obtained by the Kosolapoff technique.

An attempt to obtain diallyl iodomethylphosphonate from the chloromethylphosphonate and sodium iodide in dry acetone gave allyl iodide as the only identifiable product.

The yields and properties of the new esters are in Tables 1 and 2. Calculated values of $[R_L]_D$ were obtained from Kabachnik's atomic constants [13] for phosphorus and oxygen and Vogel's values [14] for the organic residues.

[13] Kabachnik, *Bull. Acad. Sci. U.S.S.R.*, 1948, 219; *Chem. Abs.*, 1948, **42**, 5736.
[14] Vogel, "Textbook of Practical Organic Chemistry," Longmans, London, 1948, p. 898.

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Bulk or emulsion polymerisation of tetra-allyl methylenebisphosphonate produced a resin suitable for exchange columns (to be described elsewhere).

Experimental

Some analyses (C & H) were by Mr. R. A. D. Smith of Messrs. Albright and Wilson Ltd., Oldbury; phosphorus was determined as magnesium pyrophosphate.

Allyl alcohol was dried (K_2CO_3) and redistilled; Phosphorus trichloride was redistilled after being heated under reflux to expel dissolved hydrogen chloride. Diethylaniline was purified as described by Vogel.[14] Benzene, toluene, ether, and light petroleum were dried over phosphoric oxide, decanted, redistilled, and stored over sodium wire. Methylene dibromide was treated as was allyl alcohol, and the di-iodide was decolorised over mercury before redistillation under reduced pressure.

Diethyl chloromethylphosphonate was prepared from the acid chloride which was obtained from phosphorus trichloride and paraformaldehyde (cf. ref. 15).

Bromomethylphosphonyl Dibromide.[16]—To aluminium bromide (280 g., *ca.* 1 mol.) and phosphorus tribromide (272 g., 1 mol.) in a 1 l. flask fitted with a reflux condenser, methylene dibromide (500 c.c., excess) was added portionwise with cooling. The mixture was heated cautiously, then boiled for 2 hr. It became a homogeneous red liquid. The bulk (350 c.c.) of the methylene dibromide was removed by distillation. The residual syrup solidified in a desiccator; it was added in lumps to methylene dichloride (1·2 l.) at −20° with stirring. It then disintegrated. Water (160 c.c., 8·5 mols.) was added dropwise while the mixture was kept at −20°. The precipitate was collected on sintered glass and washed twice with methylene dichloride (200 c.c.). The filtrate and washings were distilled to low bulk and degassed at the water pump, and the residue was distilled, the fraction (154—180 g., 50—60%), b. p. 130—138°/12—14 mm., being collected. Redistillation afforded pure bromomethylphosphonyl dibromide, b. p. 118—120°/7 mm., n_D^{20} 1·512.

Interaction of Sodium Diallyl Phosphite and Methylene Dihalide.—(*a*) Sodium (4·6 g., 2 mol.) was dissolved in allyl alcohol (100 c.c.) under reflux, and diallyl phosphite (32·4 g., 2 mols.) was added at 0°. Methylene di-iodide (26·8 g., 1 mol.) was added during 30 min. with stirring, and the solution then warmed at 60° for 2 hr. No precipitate was formed. The bulk of the alcohol was distilled off and residual volatile matter was removed at 60°/0·1 mm. and trapped at −80°. The combined distillate and trap contents were treated with water, and the insoluble material dried (Na_2SO_4) and distilled, giving allyl iodide (16 g.), b. p. 98—102° (*S*-thiuronium picrate m. p. and mixed m. p. 154—156°), and methylene di-iodide (4·2 g., 15·5% recovery; b. p. 79—82°/25 mm., d_4^{20} 3·32). The pasty residue (43 g.) was washed with 1 : 1 acetone–ether until free from iodide and recrystallised from methanol–ether, to give symmetrical *disodium diallyl methylenebisphosphonate* (15 g., 50%), m. p. 209—211° (Found: C, 27·8; H, 4·0; P, 21·35. $C_7H_{12}O_6P_2Na_2$ requires C, 28·0; H, 4·0; P, 20·6%). The acetone washings were treated with a large excess of water; distillation of the insoluble oil which separated gave diallyl allylphosphonate (6·5 g.), b. p. 75—78°/0·5 mm., n_D^{20} 1·4614.

(*b*) Sodium diallyl phosphite was prepared as described in (*a*) from sodium (4·6 g., 2 mols.) and diallyl hydrogen phosphite (32·4 g., 2 mols.) in allyl alcohol, after which the latter was removed at 20°/15 mm. To the dry product, toluene (200 c.c.) was added and then a portion (100 c.c.) was distilled. The process was repeated until the distillate was free from allyl alcohol. To the resulting solution, methylene dibromide (17·5 g., 1 mol.) was added in 30 min. with stirring at 0°. After about ¼—⅓ of the bromide had been added, a violet reaction set in. Sometimes the bisphosphonate was eventually obtained but the process was unreliable. Methylene dichloride gave similar results, and addition of quinol also did not give reliable reactions.

Separation of methylenebisphosphonic acid. Disodium diallyl methylenebisphosphonate (9 g.) was heated under reflux with constant-boiling hydrobromic acid (80 c.c.) for 3 hr. and the mixture was then distilled. From the distillate allyl bromide (3·8 g.) was obtained. The residual syrup was treated with more acid (50 c.c.) and sodium bromide (4·9 g., 75%) was filtered off. The filtrate was evaporated to small bulk, treated with absolute ethanol (50 c.c.),

[15] Kabachnik and Shepeleva, *Isvest. Akad. Nauk S.S.S.R.*, 1951, 185; *Chem. Abs.*, 1951, **45**, 10,191.
[16] An example of the Kinnear–Perren reaction, *J.*, 1952, 3437; Cade, A.E.R.E. Report C/M 302.
[17] Toy and Cooper, *J. Amer. Chem. Soc.*, 1954, **76**, 2191.
[18] Gerrard, *J.*, 1940, 1464.
[19] Kamai and Kukhtin, *Doklady Akad. Nauk S.S.S.R.*, 1953, **89**, 309; *Chem. Abs.*, 1954, **48**, 7540.

filtered, and evaporated, this process being repeated until the residual syrup was free from bromide. The residue, after 5 days over phosphoric oxide, gave methylenebisphosphonic acid (1·5 g.), m. p. 191—198°. Recrystallisation from *tert.*-butyl alcohol gave the pure acid [5] (0·3 g.), m. p. 201°.

Interaction of Triethyl Phosphite and Methylene Di-iodide.—(*a*) The phosphite (425 g., 2·2 mols.) and the iodide (311 g., 1 mol.) were heated together under a column (10″) containing glass helices and a condenser set for distillation. Reaction set in at 148° and the temperature rose spontaneously to 200°. Liquid distilled and the temperature was held at 190—200° until the distillation ceased (20 min.). The residue gave, by repeated redistillation, diethyl ethylphosphonate (263·6 g., 62%), b. p. 43—45°/0·1 mm., n_D^{20} 1·4150, diethyl iodomethylphosphonate (56·3 g., 7·9%), b. p. 90—100°/0·2 mm., n_D^{20} 1·4816, tetraethyl methylenebisphosphonate (81·2 g., 22%), b. p. 122—128°/0·5 mm., n_D^{20} 1·4300, and mixed fractions and residues. The primary distillate was combined with the low-boiling forerun from the main products and, after treatment with dilute hydrochloric acid and drying, gave ethyl iodide (68·6 g.), b. p. 70—73°, a mixed fraction (18·9 g.), b. p. 134—140°, and recovered methylene di-iodide (45·8 g., 14·9%), b. p. 175—182°.

(*b*) The phosphite (183 g., 2·2 mols.) was added to the iodide (134 g., 1 mol.) at 185° which was refluxing half-way up the column. The rate of addition was adjusted so that distillation (70—110°) occurred steadily and the temperature increased, finally to 220°. Heating was continued for a further 10 min. The products were ethyl iodide (128 g., 82%), b. p. 70—73°, crude diethyl ethylphosphonate (27·5 g., 15%), b. p. 35—50°/0·1 mm., n_D^{20} 1·4200, a mixed fraction containing the iodomethylphosphonate (82 g.), b. p. 80—100°/0·1 mm., n_D^{20} 1·4680, bisphosphonate (42·5 g., 29·5%), b. p. 100—105°/0·1 mm., n_D^{20} 1·4311, and a residue (32·3 g.) (Found: P, 19·8. Calc. for $C_9H_{22}O_6P_2$: P, 21·5%).

(*c*) The foregoing procedure, with the phosphite (83 g., 1 mol.) and iodide (200 g., 1·5 mol.), gave ethyl iodide (74 g., 95%), methylene di-iodide (68 g., 34%), and diethyl iodomethylphosphonate (120 g., 90%), b. p. 96—99/0·5 mm., n_D^{20} 1·5002. The residue (11 g.) contained no iodine but pure bisphosphonate was not obtained from it.

Interaction of Triethyl Phosphite and Diethyl Iodomethylphosphonate.—(*a*) When the phosphite (33·2 g., 2 mols.) and phosphonate (27·8 g., 1 mol.) were heated to 160° ebullition began but no violent reaction. Heating was continued, eventually to 180° (15 min.) where liquid began to distil (b. p. 60—80°). When distillation ceased (15 min.) the temperature was 195° at which the reactants were held for 1 hr. The distillate was ethyl iodide (2 g.) contaminated with triethyl phosphite (odour). Distillation of the reaction mixture gave: (i) forerun (4·6 g.), b. p. 40—77°/10 mm., n_D^{20} 1·4128, containing triethyl phosphite; (ii) (15·8 g.), b. p. 77—83°/10 mm., n_D^{20} 1·4150; (iii) (9·0 g.), b. p. 34—50°/0·08 mm., n_D^{20} 1·4198; (iv) (10·1 g.), b. p. 50—98°/0·08 mm., n_D^{20} 1·4748; (v) (13·9 g.), b. p. 98—135°/0·08—0·35 mm. (decomp.), n_D^{20} 1·4600; and a residue (4·8 g.) which contained iodine. From fractions (iv) and (v) combined, the iodomethylphosphonate (13·5 g., 48·6%), b. p. 80—83/0·08 mm., n_D^{20} 1·4970, was obtained by refractionation. From the forerun of this distillation combined with fractions (i)—(iii), diethyl ethylphosphonate (29·0 g., 87·4%), b. p. 43—45°/0·08 mm., n_D^{20} 1·4166, was similarly obtained. Pure tetraethyl methylenebisphosphonate was not obtained from the residues.

(*b*) The phosphite (33·9 g., 1 mol.) was added to the phosphonate (37·6 g.) at 220° as described for the preparation of the latter. The final temperature was 240°. The product included ethyl iodide (17·6 g., 83·5%) and tetraethyl methylenebisphosphonate (23 g., 59%), b. p. 123—128°/0·5 mm., n_D^{20} 1·4297. Very little iodomethylphosphonate was recovered.

Interaction of Triethyl Phosphite with Other Diethyl Halogenomethylphosphonates.—(*a*) The phosphite (40 g., 1·25 mol.) was added in 1 hr. to diethyl bromomethylphosphonate (44 g., 1 mol.) at 220—235° as described for the preparation of diethyl iodomethylphosphonate. After the usual working up, the products were ethyl bromide (14·5 g., 70%), b. p. 35—38°; diethyl ethylphosphonate (19 g., 25%), b. p. 36—40°/0·1 mm., n_D^{20} 1·412; and tetraethyl methylenebisphosphonate (263 g., 48%), b. p. 122—124/0·5 mm., n_D^{20} 1·4308.

(*b*) The phosphite (60 g., 1·1 mol.) was added to heated diethyl chloromethylphosphonate (60 g., 1 mol.) at such a rate that the temperature never fell below 220°. The addition required 14 hr. and crude ethyl chloride (4 g.) collected in a trap (0°) following the distillation receiver. There was a phosphine-like odour towards the end of the addition. The mixture was heated for a further 2 hr. but no more liquid collected in the trap. Distillation afforded crude diethyl ethylphosphonate (36·1 g., 60%), b. p. 72—90°/12 mm., n_D^{20} 1·416, and a residue (40·8 g.) which

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decomposed on further heating. Methylenebisphosphonic acid was not obtained by hydrolysis of this residue.

Interaction of Triallyl Phosphite with Methylene Di-iodide.—(*a*) The phosphite (60·6 g., 3 mol.) and iodide (26·8 g., 1 mol.) were heated. Vigorous reaction set in at 130°, and liquid distilled. After 2 hours' heating at 170—185° distillation ceased. The products, worked up as in the corresponding experiments with triethyl phosphite, were allyl iodide (14·2 g., 42·25%), b. p. 98—102°, methylene di-iodide (7·5 g., 28%), b. p. 53°/11 mm., d_4^{20} 3·31, diallyl allylphosphonate (25·5 g., 40%), b. p. 75—79°/0·6 mm., n_D^{20} 1·4640, diallyl iodomethylphosphonate (12 g.), b. p. 95—106°/0·6 mm., n_D^{20} 1·4995, tetra-allyl methylenebisphosphonate (4·0 g., 8%), b. p. 138—140°/0·6 mm., n_D^{20} 1·4675, various mixed fractions, and a residue (18 g.). The maximum yield of tetraester obtained in this way was 12%. In one experiment 8% of the iodomethylphosphonate, b. p. 100—102°/0·5 mm., n_D^{20} 1·5004, was isolated when purified at the expense of other products.

(*b*) The phosphite (40·4 g., 1 mol.) and iodide (81 g., 1·5 mol.) gave, by the method described for the corresponding diethyl ester, diallyl iodomethylphosphonate (24·8 g., 41%), b. p. 65—67°/0·05 mm., n_D^{20} 1·5015.

The author thanks Mr. J. Kennedy and Dr. E. S. Lane of A.E.R.E., Harwell, and Dr. H. Coates of Messrs. Albright and Wilson Ltd., Oldbury, for helpful suggestions and discussions.

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449. *Methylenebisphosphonates and Related Compounds. Part II.*[1] *Synthesis from α-Keto-phosphonates.*

By J. A. CADE.

By the interaction of dialkyl hydrogen phosphites and dialkyl α-keto-phosphonates in the presence of a base, tetra-alkyl 1-hydroxyalkane-1 : 1-bisphosphonates $(RO)_2PO{\cdot}CR'(OH){\cdot}PO(OR'')_2$ are formed. Some symmetrical and unsymmetrical alcohols are described.

IN an unsuccessful attempt to prepare diethyl acetylphosphonate (III) by interaction of sodium diethyl phosphite and acetyl chloride, Arbusov and Azanovskaya[2] obtained as the main product of the reaction, tetraethyl 1-ethoxycarbonylethylidenebisphosphonate (V). They showed that the reactions involved were (1)—(3), for by starting with keto-phosphonate (III), sodium dialkyl phosphite, and acetyl chloride, the sequence (2)—(3) could be realised independently:

$$\underset{\text{(I)}}{(EtO)_2PO{\cdot}Na} + \underset{\text{(II)}}{AcCl} \longrightarrow \underset{\text{(III)}}{(EtO)_2P(O){\cdot}CO{\cdot}CH_3} + NaCl \quad \ldots\ldots\ldots (1)$$

$$\text{(I)} + \text{(III)} \longrightarrow (EtO)_2PO{-}\underset{\underset{\text{(IV)}\quad ONa}{|}}{\overset{\overset{Me}{|}}{C}}{-}PO(OEt)_2 \quad \ldots\ldots\ldots (2)$$

$$\text{(IV)} + \text{(II)} \longrightarrow (EtO)_2PO{-}\underset{\underset{OAc\quad \text{(V)}}{|}}{\overset{\overset{Me}{|}}{C}}{-}PO(OEt)_2 + NaCl \quad \ldots\ldots\ldots (3)$$

The intermediate alcohol corresponding to (IV) was not isolated, but recently examples of such compounds prepared by this method but with an organic base in place of sodium have been reported.[3] Some new 1 : 1-bisphosphono-alcohols, $(RO)_2PO{\cdot}CR'(OH){\cdot}PO(OR)_2$, are

[1] Part I, preceding paper.
[2] Arbusov and Azanovskaya, *Doklady Akad. Nauk S.S.S.R.*, 1947, **58**, 1961.
[3] McConnell and Coover, *J. Amer. Chem. Soc.*, 1956, **78**, 4450.

now described, and it has been shown that the reaction can be effected with much less than one equivalent of sodium.[4] A trace of organic tertiary base could also be employed to initiate the reaction but offered no advantage over sodium because acidic by-products tended to hold the base back until the desired product was distilling, whereupon it was liberated and contaminated the latter.

The new alcohols and their physical constants are listed in Table 1; Table 2 contains analytical data. Most of the are colourless, practically odourless liquids. Lorentz–Lorenz molar refractivities $[R_L]_D$, were deduced from the observed physical constants and provide evidence of composition. Calculated values were computed from the atomic values for oxygen and phosphorus derived by Kabachnik [5] and group values of the organic residues given by Vogel.[6] The infrared spectra of the compounds will be described in a subsequent paper.

The stated crude yields were reproducible for reactions carried out on an approximately 0·25 molar scale. On a larger scale, the yields, in particular of the unsaturated esters,

TABLE 1.

No.	Compound R	R′	R″	Yield (%) *	B. p./mm.	n_D^t	d_4^t	$t°$
1 †	Me	Me	Me	30	126—128°/0·07	1·4300	1·269	25
2 †	Et	Me	Et	67	125°/0·06	1·4350	1·154	20
3	A	Me	A	55	137°/0·15	1·4615	1·137	20
4 †	Pr^i	Me	Pr^i	63	115°/0·06	1·4326	1·072	20
5	Bu	Me	Bu	72	159°/0·12	1·4364	1·039	25
6 †	Me	Me	Et	35	124—128°/0·07	1·433	—	20
7	Et	Me	A	42	126—128°/0·01	1·455	—	20
8 †	Et	Me	Pr^i	40	124—129°/0·1	1·434	—	20
9	Et	Me	Bu	35	130°/0·05	1·4370	1·087	25
10	Me	Ph	Me	—	‡	—	—	—
11	Et	Ph	Et	72	149°/0·07	1·4798	1·180	25
12	Bu	Ph	Bu	50	180—184°/0·1	1·4786	1·064	20
13 †	Me	X	Me	36	140—142°/0·1	1·436	—	25
14 †	Et	Y	Et	—	‡	—	—	—

A = allyl, CH_2:$CH{\cdot}CH_2$–; X = propenyl, CHMe:CH–; Y = CHMe:CH·CH:CH–.
* Crude. Purification before characterisation was at expense of yield. † H_2O-miscible. ‡ Does not distil.

TABLE 2.

Compound	Formula	Found (%) C	H	P	$[R_L]_D$	Required (%) C	H	P	$[R_L]_D$
1	$C_6H_{16}O_7P_2$	27·5	6·1	23·4	53·36	27·5	6·15	23·6	52·92
2	$C_{18}H_{24}O_7P_2$	38·55	7·7	20·3	72·0	37·75	7·6	19·5	71·52
3	$C_{14}H_{24}O_7P_2$	45·7	6·7	16·7	88·48	45·9	6·6	16·9	88·40
4	$C_{14}H_{28}O_7P_2$	44·4	8·6	16·7	90·64	44·9	8·6	16·55	90·24
5	$C_{18}H_{40}O_7P_2$	50·0	9·3	14·3	108·43	50·2	9·4	14·4	108·68
6	$C_6H_{20}O_7P_2$	—	—	20·9	*	—	—	21·35	—
7	$C_{12}H_{24}O_7P_2$	—	—	18·0	*	—	—	18·1	—
8	$C_{12}H_{28}O_7P_2$	—	—	17·3	*	—	—	17·9	—
9	$C_{14}H_{32}O_7P_2$	44·6	8·5	16·3	90·22	44·9	8·6	16·55	90·10
10	$C_{11}H_{19}O_7P_2$	—	—	18·9	*	—	—	19·1	—
11	$C_{18}H_{36}O_7P_2$	47·3	6·9	16·3	91·54	47·4	6·9	16·3	91·23
12	$C_{32}H_{42}O_7P_2$	58·7	8·7	11·75	131·15	56·1	8·6	12·6	128·39
13	$C_8H_{18}O_7P_2$	32·5	6·8	20·9	*	33·3	6·3	21·5	—
14	$C_{14}H_{28}O_7P_2$	46·2	7·6	15·35	*	45·4	7·6	16·7	—

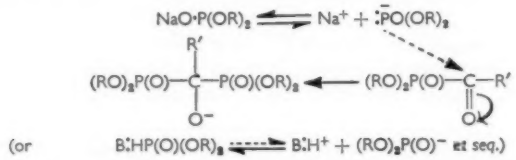
* Insufficiently pure ester available.

were lower, and larger residues were obtained, probably as a result of the prolonged heating necessary to distil proportionately larger quantities. Those compounds in which R, R′, or R″ were unsaturated were of particular interest since resins containing the essential

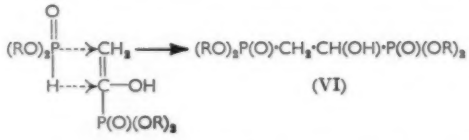
[4] Cade, A.E.R.E. Report, C/R 2012, 1957.
[5] Kabachnik, *Bull. Acad. Sci. U.S.S.R.*, 1948, 219.
[6] Vogel, " Textbook of Practical Organic Chemistry," Longmans, London, 1948, p. 898.

–P(O)·C·P(O)– bridge could be derived from them,[1] but an opportunity was taken of investigating the general applicability of the method.

Evidence concerning the mechanism of this type of reaction is not yet available but, from the qualitative observations that the reaction is base-catalysed and that the higher alkyl phosphites react more sluggishly, it may be provisionally depicted as a pre-ionisation followed by nucleophilic attack,[3] the latter being rate-determining:



The possibility that for acetylphosphonates the process may be a Michael-type addition resulting in formation of an ethylenebisphosphonate (VI), was not overlooked,[7] although keto-enol tautomerism in α-keto-phosphonates has not yet been established:



The reaction between diethyl acetylphosphonate and dibutyl hydrogen phosphite was complicated by transesterification, as was that between diethyl hydrogen phosphite and dibutyl acetylphosphonate. Each reaction, however, gave among its products the same dibutyl diethyl 1-hydroxyethylidenebisphosphonate. The identity of the products was based on the concurrence of physical properties and analysis, and the virtually identical infrared spectra.

This observation is good evidence that addition occurs across the double bond of the carbonyl group. Further, benzoylphosphonates, which cannot exhibit keto–enol tautomerism, readily undergo the reaction.

Experimental

α-Keto-phosphonates.—The esters were prepared in the usual manner [8] by adding trialkyl phosphite (1 mol.) to acid chloride (1·1 mol.) at −10°, allowing the mixture to attain room temperature, and distilling the products. New keto-phosphonates were: *Diallyl* (50—67% yield), b. p. 71°/0·25 mm., n_D^{20} 1·4534, d_4^{20} 1·105 (Found: C, 47·0; H, 6·4; P, 15·1%; $[R_L]_D$ 50·00. $C_8H_{13}O_4P$ requires C, 47·1; H, 6·4; P, 15·2%; $[R_L]_D$ 49·17), and *di-isopropyl acetylphosphonate* (62—72%), b. p. 56°/0·1 mm., n_D^{20} 1·419 (Found: P, 14·8. $C_8H_{17}O_4P$ requires P, 14·9%); *dibutyl benzoylphosphonate* (65%), b. p. 160—164°/0·1 mm., n_D^{20} 1·4975 (Found: P, 10·4. $C_{15}H_{23}O_4P$ requires P, 10·4%); *dimethyl crotonoylphosphonate* (30%), b. p. 65—68°/0·05 mm., n_D^{25} 1·463 (Found: P, 17·3. $C_6H_{11}O_4P$ requires P, 17·4%); *diethyl hexa-2 : 4-dienoylphosphonate* (49%), b. p. 106—110°/0·07 mm., n_D^{25} 1·503 (Found: P, 13·0. $C_{10}H_{17}O_4P$ requires P, 13·3%).

Dialkyl Hydrogen Phosphites.—Redistilled commercial products were used, but diallyl hydrogen phosphite was prepared as described in Part I.[1]

Tetra-alkyl 1-Hydroxyalkylidenebisphosphonates.—To a mixture of dialkyl acetylphosphonate (0·25 mole) and excess of dialkyl phosphite (0·3 mole) was added sodium (0·01 g.-atom) dissolved in the minimum quantity of alcohol having the same alkyl group as that of the hydrogen phosphite. This reduced the chance of transesterification in preparation of unsymmetrical esters in which R ≠ R′. The temperature of the mixture rose spontaneously by 20—60° and was

[7] Kennedy, personal communication.
[8] Kosolapoff, "Organophosphorus Compounds," Wiley, New York, 1950, p. 122.

kept about 50° higher than the maximum initially attained for 2—4 hr. The exothermicity was governed by the nature of the alkyl groups; thus the di-isopropyl esters reacted more sluggishly than the ethyl esters in equivalent conditions. After reaction volatile matter was removed and the residue was separated into two main fractions by distillation at low pressure. Redistillation of the higher-boiling fraction afforded the pure tetra-ester in 50—70% yields.

An alternative procedure useful for obtaining higher analogues (especially where R′ = Ph) was to add the keto-phosphonate to a pre-prepared solution in benzene of an equivalent of the sodium dialkyl phosphite, heat the whole under reflux for 2—4 hr., and separate the product after aqueous treatment which removed acidic impurities as the sodium salts.

This work was carried out in the Research Laboratories of Messrs. Albright and Wilson Ltd., of Oldbury, during an extra-mural contract with that company in 1955—56. The author thanks Mr. R. A. D. Smith (for carbon and hydrogen analyses), Mr. J. A. Chambers (for most of the phosphorus analyses), and Dr. H. Coates (for stimulating discussions and advice), also Mr. J. Kennedy and Dr. E. S. Lane of A.E.R.E., Harwell.

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450. *The Reaction between Ammonia and Transition-metal Halides. Part VI.*[1] *The Reaction of Ammonia with Tungsten*(VI) *Chloride.*

By G. W. A. FOWLES and B. P. OSBORNE.

Tungsten(VI) chloride reacts with liquid ammonia to give a series of ammoniates, but subsequently undergoes ammonolysis with the formation of various ammonobasic tungsten(VI) chlorides. Compounds of overall composition $WCl_6.4NH_3$ and $WCl_6.6NH_3$, which are formed by passing ammonia gas through a solution of tungsten(VI) chloride in carbon tetrachloride, contain the ammonobasic products $WCl_5(NH_2)$ and $WCl_4(NH_2)_2$, respectively; the thermal decomposition of these compounds is discussed.

THE reaction of ammonia with transition-metal halides has been studied in detail in recent years;[1] covalent halides of the metals in their higher-valency states are ammonolysed in liquid ammonia to give an ammonobasic metal halide and the appropriate ammonium halide, *e.g.*, $TiCl_4 \longrightarrow TiCl(NH_2)_3.2NH_3 + 3NH_4Cl$.

Little work has been done on the analogous reactions of the molybdenum and tungsten halides, however, apart from that by Bergström,[2] who cursorily examined the ammonolysis of several halides and reported the formation of ammonobasic metal halides of indefinite composition. Spacu [3] studied the tungsten(VI) chloride–ammonia system tensimetrically at −75°, and then removed associated ammonia at various temperatures up to 0°; except for establishing the formation of a product of overall composition approximating to $WCl_6.6NH_3$, this investigation gave little information about the reaction.

Extending our studies on ammonolysis, we now report on the reaction of tungsten(VI) chloride with liquid ammonia (as investigated by both tensimetric and washing experiments) and with gaseous ammonia (when passed through a solution of the halide in carbon tetrachloride).

EXPERIMENTAL

Materials.—Liquid ammonia (from Imperial Chemical Industries Limited) was dried (Na) before distillation into the apparatus *in vacuo*. Tungsten(VI) chloride was prepared by the action of chlorine on pure tungsten powder (Messrs. Johnson and Matthey) at 600° in a quartz tube; traces of tungsten(VI) oxychlorides were also formed, but were sublimed off *in vacuo*

[1] Part V, Fowles and Nicholls, *J.*, 1959, 990.
[2] Bergström, *J. Amer. Chem. Soc.*, 1925, **47**, 2317.
[3] Spacu, *Bull. Sect. sci. Acad. Roumaine*, 1940, **22**, 329.

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(Found: Cl, 53·4. Calc. for WCl_6: Cl, 53·6%). Carbon tetrachloride ("AnalaR") was dried over, and distilled from, phosphoric oxide immediately before use.

Analyses.—Nitrogen was determined as ammonia by distillation from alkaline solution into hydrochloric acid followed by titration with standard sodium hydroxide (B.D.H. 4·5 indicator). Chlorine was determined potentiometrically by titration with silver nitrate, in a sodium acetate–acetic acid buffered solution, silver–silver chloride and mercurous sulphate electrodes being used. Tungsten was determined by reduction to the tervalent state with lead amalgam, followed by addition of ferric alum and titration with potassium dichromate with sodium diphenylaminesulphonate as indicator; a modified form of Holt and Gray's apparatus [4] was used.

Magnetic-moment Measurements.—These were made at room temperature on a Gouy-type balance, at a field strength of 8000 gauss.

Reactions and Tensimetric Studies.—These were carried out in the usual type of all-glass closed vacuum system,[5,6] with joints and stopcocks lubricated with Silicone grease.

(i) *Passage of ammonia vapour through a solution of tungsten*(VI) *chloride in carbon tetrachloride.* Tungsten(VI) chloride dissolved in carbon tetrachloride to give a red solution, and when ammonia vapour, in a stream of well-dried oxygen-free nitrogen, was passed through the solution, a green precipitate formed, but this became chocolate-brown with excess of ammonia. The green and the brown product were isolated by stopping the reaction at the appropriate stage, filtering *in vacuo*, and washing out any unchanged tungsten(VI) chloride with carbon tetrachloride. The products were analysed after removal of excess of carbon tetrachloride at the pump [Found, for green product: $WCl_6 : NH_3 = 1·00 : 4·20$ (1·00 : 4·35). Found, for brown product: $WCl_6 : NH_3 = 1·00 : 6·04$ (1·00 : 5·95)]. Both products were heated *in vacuo* from room temperature to 200°, and any evolved products were condensed and examined. The results are in Table 1.

TABLE 1. *Thermal decomposition of* $WCl_6,4NH_3$ *and* $WCl_6,6NH_3$.

	$WCl_6,4NH_3$	$WCl_6,6NH_3$
* Gas liberated below 130°	—	1 mole NH_3
* Gas liberated above 130°	1·8 moles HCl	1 mole HCl
NH_4Cl found	2·0 moles	2·84 moles
Analysis of black residue remaining at 200° (W : Cl : N)	1·0 : 2·05 : 1·60	1·0 : 2·18 : 1·82

* The liberated gas was identified by its vapour density and by simple chemical tests.

(ii) *Washing procedure.* Tungsten(VI) chloride largely dissolved in liquid ammonia to give a deep reddish-brown solution, although a small amount of brown solid remained undissolved even on prolonged washing with liquid ammonia. The composition of this residue, which contained about 10% of the original tungsten, varied from experiment to experiment within the limits W : Cl : N = 1·0 : 2·5 : 3·4 and 1·0 : 1·9 : 3·8 although it approached the latter ratio in the majority of cases. The solid was diamagnetic.

When excess of ammonia was evaporated from the filtrate, a heterogeneous solid remained, which after pumping for several hours was hydrolysed *in situ* and analysed. In expressing the results of the analysis of several products (cf. Table 2) we have assumed that the soluble

TABLE 2. *Soluble portion.*

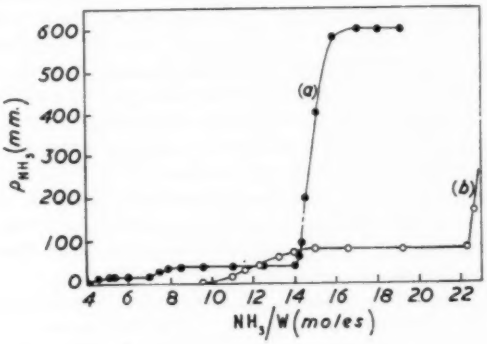
	N : Cl ratio, W being assumed to be present as:	
Run No.	$WCl_3(NH_2)_3$	$WCl_4(NH_2)_2$
1	1·00 : 0·72	1·00 : 0·96
2	1·00 : 0·68	1·00 : 1·11
3	1·00 : 0·65	1·00 : 1·02

portion is a mixture of ammonium chloride and an ammonobasic tungsten(VI) chloride, so that from the determined tungsten content, the associated nitrogen and chlorine required for each of the more likely compounds can be calculated. The N : Cl ratio for the remaining nitrogen

[4] Holt and Gray, *Ind. Eng. Chem., Anal.*, 1940, **12**, 144.
[5] Fowles and Pollard, *J.*, 1953, 4128.
[6] *Idem*, *J.*, 1953, 2588.

and chlorine (cf. Table 2) should then be 1 : 1, corresponding to ammonium chloride. A tensimetric run on the soluble portion–ammonia system showed the presence of ammonium chloride.

(iii) *Tensimetric experiments.* A known excess of ammonia was condensed on a known weight of the halide at liquid-oxygen temperatures; a very vigorous reaction took place when the reaction vessel was surrounded with a slush bath at −36°, and the vessel was shattered on several occasions. The reaction was made less energetic by using a detachable vessel, and shaking constantly while the contents warmed to −36° during several hours; at −80° an orange product formed, which later became brown. The tensimetric plot subsequently obtained



at −36° [(*a*) in Figure] showed two univariant portions with pressures of 40 mm. and 19 mm. which extended over composition ranges of 6 and 2 moles of NH_3/mole of WCl_6, respectively. From this plot it is evident that a bivariant system, probably representing a general desorption of ammonia, is also present.

TABLE 3. *Dissociation pressures of the " A " and " B " ammoniates of* WCl_6.

	" A " ammoniate			" B " ammoniate			
Temp.	−38·9°	−22·0°	−11·0°	−64·5°	−49·0°	−38·0°	−28·0°
Press. (mm.)	16·0	56·0	122·0	5·0	19·0	43·0	91·0

The dissociation pressures of these ammoniates (referred to in future as " A " and " B ") were measured over a 30° temperature range (Table 3), and from the integrated form of the van't Hoff equation ΔH values of 8·10 and 8·90 kcal./mole, respectively, were calculated. The tensimetric curves were reproducible (in ten experiments) to within 0·4 mole of NH_3/mole of WCl_6. The overall composition of the solid remaining after removal of excess of ammonia at −36° was $WCl_6,4NH_3$.

Despite constant shaking and slow attainment of the equilibrium temperature (−36°), a violent reaction still occurred in about a quarter of the experiments, and, as with experiments in which the reaction vessel was warmed directly to −36°, the product was heterogeneous and contained white particles. In some eight experiments in which the reaction vessel survived the initial reaction, tensimetric plots were made in the usual way, and in every experiment a new univariant step appeared in the curve. This step occurred at a pressure corresponding to the dissociation $NH_4Cl,3NH_3 \rightleftharpoons NH_4Cl + 3NH_3$, showing that ammonium chloride was now present. The amount of ammonium chloride triammoniate found varied, and was in inverse proportion to the amount of " A " and " B " ammoniate present, showing that these ammoniates disappeared as ammonium chloride was formed. In limiting experiments, in which the " A " and " B " ammoniates were no longer present [(*b*) in Fig.], the univariant portion corresponding to the dissociation of $NH_4Cl,3NH_3$ had a length of about 8 moles of NH_3/mole of WCl_6, showing the presence of 2—3 mol. of ammonium chloride. On removal of excess of ammonia (at −36°) the remaining product had an overall analysis of $WCl_6,9NH_3$.

The compositions of the final products of tensimetric runs were confirmed by direct analysis.

Discussion

Although the two compounds obtained by passing ammonia gas through a solution of tungsten(VI) chloride in carbon tetrachloride had overall compositions approximating to tetra- and hexa-ammoniates, it is unlikely that they are simple adducts, because this implies covalencies of 10 and 12 for the tungsten atom. A covalency of 12 is plainly impossible, but it has been suggested [7] that the tungsten atom achieves a covalency of 10 in such complex anions as $[W(CN)_6(NH_3)_2]^{2-}$. There are three alternatives to considering these products as simple adducts: (1) The covalency may be limited to 8 by considering only two ammonia molecules to be bonded directly to the tungsten atom, with the remaining molecules more loosely held by " secondary bonding," rather like that in the ammoniates formed by the cobaltammine ions; [8] (2) cationic complexes may be formed, *e.g.*, $[WCl_4(NH_3)_4]^{2+}2Cl^-$ and $[WCl_2(NH_3)_6]^{4+}4Cl^-$; (3) ammonolysis has taken place, so that the products are mixtures of ammonobasic tungsten(VI) chlorides and ammonium chloride. The first two suggestions must be ruled out because an uncharged adduct such as $WCl_6,2NH_3$ could hardly attract significantly further ammonia molecules at room temperature, and sexavalent tungsten is too acidic to form cationic complexes.

At room temperature, it is more likely that ammonolysis has taken place, and if, moreover, the tetra- and hexa-ammoniates are formulated as mixtures containing one and two moles of ammonium chloride respectively, then their thermal decomposition *in vacuo* is readily interpreted.

The formation of ammonium chloride at 130° in both decompositions implies that ammonia and hydrogen chloride are being liberated simultaneously and recombining on the cooler parts of the reaction vessel, since pre-formed ammonium chloride would not sublime *in vacuo* below 180—200°.

The tetra-ammoniate would decompose according to the sequence:

$$NH_4Cl + WCl_5(NH_3),2NH_3 \xrightarrow{(1)} NH_4Cl + WCl_5(NH_3),NH_3 + NH_3$$

$$NH_4Cl + WCl_5(NH_3),NH_3 \xrightarrow{(2)} NH_4Cl + WCl_4(NH_2)_2 + HCl$$

$$NH_4Cl + WCl_4(NH_2)_2 + HCl \longrightarrow NH_4Cl + WCl_3(NH_2)_3 + 2HCl$$

} recombine giving NH_4Cl

As soon as reaction (1) has taken place, reaction (2) follows, so that 1 mol. of ammonium chloride is formed, and together with that present initially in the mixture will give a total sublimate of 2 mol. of ammonium chloride at 200°.

The hexa-ammoniate differs from the tetra-ammoniate in liberating 1 mol. of ammonia around 100° and only 1 mol. of hydrogen chloride above 130°, and its thermal decomposition is probably:

$$2NH_4Cl + WCl_4(NH_2)_2,2NH_3 \longrightarrow 2NH_4Cl + WCl_4(NH_2)_2,NH_3 + NH_3$$

$$2NH_4Cl + WCl_4(NH_2)_2,NH_3 \longrightarrow 2NH_4Cl + WCl_4(NH_2)_2 + NH_3$$

$$2NH_4Cl + WCl_4(NH_2)_2 + NH_3 \longrightarrow 2NH_4Cl + WCl_3(NH_2)(NH) + HCl$$

$$2NH_4Cl + WCl_3(NH_2)(NH) + HCl \longrightarrow 2NH_4Cl + WCl_2(NH)_2 + HCl$$

} recombine giving NH_4Cl

The final product of either decomposition would be $WCl_2(NH)_2$. Analysis shows that this is certainly the major product, and the rather low nitrogen content is attributed to some side reaction.

The low-temperature reactions with liquid ammonia are essentially of two distinct types, first, those in which only addition ammoniates are formed, and secondly, those in which ammonolysis takes place. The first type of reaction takes place when tungsten(VI) halide and ammonia are allowed to warm slowly to −36°, and on these

[7] Jakób and Jakób, *Roczniki Chem.*, 1952, **26**, 492.
[8] Spacu and Voichescu, *Z. anorg. Chem.*, 1940, **243**, 268.

occasions the tensimetric curves show only the presence of two simple ammoniates, and the final formation of a tetra-ammoniate when excess of ammonia is removed at the reaction temperature. This tetra-ammoniate is quite different from that obtained in the flow runs, in being steel-blue, rather like tungsten(VI) chloride itself, and in gradually losing some of this ammonia on warming to room temperature and above. It is not perhaps unreasonable to consider this low-temperature product to be a simple adduct in which the tungsten atom achieves a covalency of 10.

This is in agreement with the absence of ammonium chloride triammoniate from the tensimetric plots. Higher ammoniates (" A " and " B ") are also formed, although the ease with which the additional ammonia is removed at −36° and the ΔH values of 8—9 kcal./mole show that the ammonia is very weakly held, as with the higher ammoniates of many metal halides.

In the violent reaction, ammonolysis is indicated by the heterogeneous nature of the product and confirmed by the tensimetric experiments. Moreover, the reaction products now contain smaller amounts of the " A " and " B " ammoniates—in inverse proportion to the amount of ammonium chloride present—showing that the compound which forms these ammoniates disappears as ammonium chloride is formed. The probable explanation is that, although tungsten(VI) chloride initially forms ammoniates (in the tranquil reaction), it subsequently undergoes ammonolysis with considerable violence. The maximum ammonolysis observed in the tensimetric experiments (that when the " A " and " B " ammoniates were no longer present) [cf. Fig. (*b*)] corresponds to an equilibrium position in which 2—3 tungsten–chlorine bonds have been ammonolysed.

When tungsten(VI) chloride is exposed to a large excess of liquid ammonia at its boiling point, then ammonolysis is evidently much more complete. Most of the product is soluble, and analysis of this portion shows it to be a mixture of excess of ammonium chloride and the ammonobasic tungsten(VI) chloride, $WCl_4(NH_2)_2$; the small insoluble portion appears to be a mixture of $WCl_3(NH_2)_3$ and $WCl_2(NH_2)_4$. It seems likely that when $WCl_4(NH_2)_2$ is formed, it is complexed by the ammonium chloride with the formation of a soluble anionic tungsten species such as $[WCl_6(NH_2)_2]^{2-}$, similar to the behaviour in the titanium(VI) iodide–ammonia system.[1] The more highly ammonolysed products remain undissolved, since most of the ammonium chloride is removed in the first washing. The formation of a complex anion in liquid ammonia also explains Bergström's observation that, although the product is entirely soluble in concentrated solutions, an ammonobasic tungsten(IV) chloride is precipitated on dilution, since complex formation would take place most readily in a high concentration of chloride ion. When the liquid ammonia is removed, as in the tensimetric experiments, then the complex anions will be unstable, so that the ammonium chloride is available to form its normal triammoniate. The tungsten-blue colour which developed when the products of the tungsten(VI) chloride–ammonia reaction were placed in acid solution suggests that some reduction might have taken place, but the diamagnetism of the products shows that reduction is in fact insignificant.

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SOUTHAMPTON UNIVERSITY. [*Received, November 17th,* 1958.]

[1] Biltz, *Z. anorg. Chem.*, 1923, **130**, 93.

XUM

451. *The Reaction of 4-Hydroxycinnoline-3-carboxylic Acid with Pyridine and Acetic Anhydride.*

By J. S. Morley.

The constitution of the product formed by warming together the reactants named in the title has been shown to be (II; R′ = H) and not (IIS) * as reported previously.[1] The degradative work involved in this proof (see the "New Scheme") illustrated the ready nuclear halogenation of 2-arylazopyridines by aqueous halogen acids (VII ⟶ VIII and IX). Syntheses of 2-*o*-carboxyphenylazopyridine (VII) (involving condensation of *o*-nitrosobenzoic acid with 2-aminopyridine in 50% aqueous sodium hydroxide), its 4-chloro-derivative (VIII), the indazolone (IX), and a number of intermediate or related products are described.

In 1946, Schofield and Simpson [1] found that treatment of 4-hydroxycinnoline-3-carboxylic acid (I; R′ = H) (1 part) with a mixture of pyridine (4·5 parts) and acetic anhydride (6·5 parts) produced a substance, m. p. 217°, of formula $C_{16}H_{11}O_3N_3$, in good yield, according to the equation $C_9H_6O_3N_2 + C_5H_5N + Ac_2O \longrightarrow C_{16}H_{11}O_3N_3 + AcOH + H_2O$. Using the production of "Reissert" compounds from quinoline, acid chlorides, and potassium cyanide as a model, they formulated the product as a resonance hybrid of three species with the carbonium form (IIS) * making a major contribution. The substance was highly reactive and various reactions were described; when, for example, it was refluxed with the lower alcohols, or with aniline in benzene, it gave a series of amphoteric adducts, which were assigned the structures (IIIS; R = Me, Et, and Pr^i; and also NHPh in place of OR). Schofield and Simpson attempted to verify these structures by degradation, which they considered to follow the scheme given as "Schofield and Simpson's Scheme." The key product, produced from several of the compounds in the series, was a yellow base, $C_{13}H_9N_3,2H_2O$, m. p. 152·5—153·5°, which Schofield and Simpson formulated as 4-2′-pyridylcinnoline (VIS). It was, however, difficult to explain the ease of oxidation of this base to an acid, $C_{12}H_9O_2N_3$, m. p. 146—147° (formulated as VIIS), and the conversion of this by boiling 5N-hydrochloric acid into a mixture of an orange-pink amphoteric compound, m. p. 195°, and a colourless weak ampholyte, m. p. 254° (formulated as VIIIS and IXS respectively). Doubt was later cast on the whole proposed scheme by the synthesis [2] of 4-2′-pyridylcinnoline (VIS), which was not identical with the base, m. p. 152·5—153·5°, as postulated.

An alternative explanation seemed possible. Formation of the initial product, $C_{16}H_{11}O_3N_3$, appeared analogous to the production of "Besthorn's Red" (X) from similar reactants.[3,4] The resulting expression (II; R′ = H) explained the various transformations satisfactorily. Thus the action of alcohols would lead to β-keto-esters (III; R = Me, Et, Pr^i) (these substances were soluble in alkali and gave characteristic red-violet ferric reactions), and other products in the scheme could be formulated as (IV) and (V).

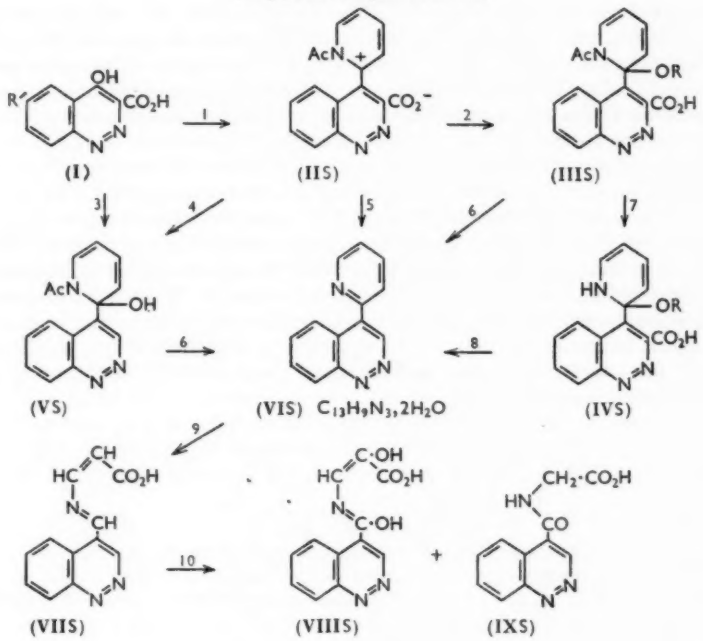
However, it was still difficult to assign a constitution to the yellow base (VIS), m. p. 152·5—153·5°. Its formula, $C_{13}H_9N_3,2H_2O$ was considered by Schofield and Simpson to be "eventually proved by analysis of the picrate, which was solvent-free; the styphnate was monohydrated, and the hydrochloride was a dihydrate." Nevertheless, their analytical figures agreed equally with a formula $C_{13}H_9ON_3,H_2O$ (the hydrochloride as monohydrate, and picrate and styphnate anhydrous) with the possible exception of those for the picrate. Our own figures for the picrate differed somewhat from Schofield and

* The use, in this paper, of the suffix S against a formula number, *e.g.* (IIS), denotes a structure proposed by Schofield and Simpson [1] for a substance now shown to have the structure carrying the unmodified formula number, *e.g.*, (II).

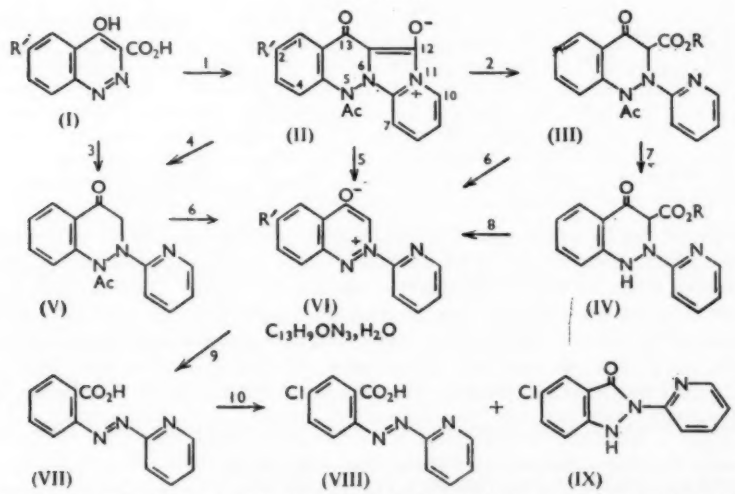
[1] Schofield and Simpson, *J.*, 1946, 472.
[2] Schofield, *J.*, 1949, 2408.
[3] Besthorn and Ibele, *Ber.*, 1904, **37**, 1236; 1905, **38**, 2127.
[4] Besthorn, *Ber.*, 1913, **46**, 2762.

Simpson's and agreed closely with a formulation $C_{13}H_9ON_3$ for the base. Moreover, after drying for 16 hours over phosphoric oxide at 60° *in vacuo*, the base gave figures corresponding to the anhydrous formula, $C_{13}H_9ON_3$. The betaine structure (VI; R′ = H) then

Schofield and Simpson's Scheme.



New Scheme.

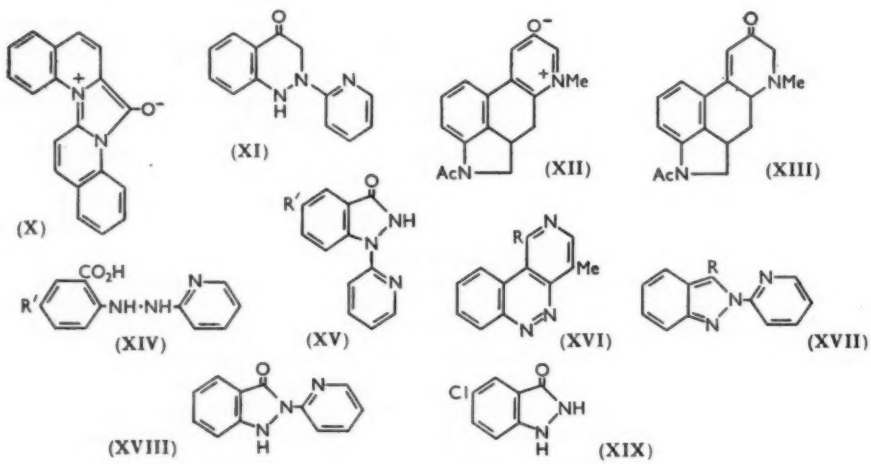


Reagents: 1, C_5H_5N–Ac_2O (4·5 + 6·5 pts.). 2, ROH. 3, C_5H_5N–Ac_2O (3 + 1 pt.). 4, C_5H_5N or H_2O. 5, Hot dil. HCl. 6, Hot dil. HCl or NaOH. 7, ROH–H_2SO_4. 8, Hot NaOH. 9, $KMnO_4$. 10, 5N-HCl.

became possible for the base. Its formation, by oxidation of the hypothetical precursor (XI) (which can arise from II, III, IV, or V by normal hydrolytic processes), is not abnormal in view of the ready oxidation of dihydrocinnolines to cinnolines, and a somewhat similar betaine (XII) is readily produced by the dehydrogenation of (XIII) and crystallises as a hydrate.[5]

The oxidation of the base became readily understood on the basis of this proposed structure. The expected oxidation product, 2-*o*-carboxyphenylazopyridine (VII), possessed the empirical formula assigned to the acid (VIIS) and its expected properties agreed well with those described by Schofield and Simpson. Moreover, the constitution of the products (VIIS) and (IXS) of the action of boiling 5N-hydrochloric acid became clear. Under such conditions, 4-phenylazopyridine gives 4-(*p*-chlorophenylhydrazino)pyridine,[6] and similar nuclear halogenations of 2-arylazopyridines have been reported by Colonna *et al.*[7,8] By analogy, (VII) should give 2-(2-carboxy-4-chlorophenylhydrazino)pyridine (XIV; R′ = Cl) which by cyclisation could give the indazole (IX), and by oxidation the azo-compound (VIII). The presence of chlorine in the two products was not suspected in the original work, but it is present and the analyses agree with the new structures postulated.

Our interpretations are shown in the "New Scheme." To test its correctness the pyridine–acetic anhydride reaction was applied to 6-chloro-4-hydroxycinnoline-3-carboxylic acid. A chloro-zwitterion (II; R′ = Cl) was thereby obtained which, by degradations analogous to (II ⟶ VI, and VI ⟶ VII), gave a chloro-acid corresponding to (VII), which was identical with (VIII).



Final proof was by synthesis. 2-*o*-Carboxyphenylazopyridine (VII) was obtained by condensing *o*-nitrosobenzoic acid with 2-aminopyridine in 50% aqueous sodium hydroxide (after abortive attempts to perform this reaction in acetic acid).[9] 5-Chloro-2-2′-pyridyl-3-indazolone (IX) was obtained as one product on condensation of 5-chloro-2-hydrazinobenzoic acid with 2-chloropyridine and was identical with Schofield and Simpson's colourless ampholyte, m. p. 254° (as were the monomethyl derivatives). The 1-2′-pyridyl isomer (XV; R′ = Cl) was a second product from the latter condensation. Reducing the acid

[5] Kornfeld, Fornefeld, Kline, Mann, Morrison, Jones, and Woodward, *J. Amer. Chem. Soc.*, 1956, **78**, 3094, 3111.
[6] Koenigs, Freigang, Lobmayer, and Zscharn, *Ber.*, 1926, **59**, 321.
[7] Colonna and Risaliti, *Gazzetta*, 1955, **85**, 1148; 1956, **86**, 288.
[8] Colonna, Risaliti, and Serra, *ibid.*, 1955, **85**, 1508.
[9] Cf. Campbell, Henderson, and Taylor, *J.*, 1953, 281.

(VIII) catalytically or by stannous chloride or thiol compounds gave 2-(2-carboxy-5-chlorophenylhydrazino)pyridine (XIV; R′ = Cl), the hydrochloride of which, when heated in ethanol at 170—180°, likewise gave the indazole (IX).

A further point deserves mention. Degradation of the ketone (V) to the betaine (VI) by alkaline hydrolysis gave two by-products to which Schofield and Simpson [1] assigned the structures (XVI; R = OH and CO_2H). When the analogy of the hypothetical precursor (XI) [arising from (V) by a normal hydrolysis] to indoxyl is considered, oxidation by air in alkaline media may be considered likely. Ring contraction, by unexceptional processes, of the oxidation products could then lead to indazoles. One of Schofield and Simpson's by-products was an acid, m. p. 169—170° (decomp.). This is probably 2-2′-pyridylindazole-3-carboxylic acid (XVII; R = CO_2H), and the derived base, obtained by decarboxylation, is probably (XVII; R = H). The other by-product, an ampholyte, m. p. 186·5—187·5°, was identified as 2-2′-pyridyl-3-indazolone (XVIII); it was synthesised by heating the hydrochloride of 2-*o*-carboxyphenylhydrazinopyridine (XIV; R = H) [obtained by reduction of (VII)] in ethanol at 170—180°. *o*-Hydrazinobenzoic acid with 2-chloropyridine gave only one pyridylindazolone (the corresponding reaction of 5-chloro-2-hydrazinobenzoic acid led to both isomers), which was not identical with (XVII; R = OH) and must therefore be the 1-isomer (XV; R′ = H); this conclusion was supported by the infrared absorption spectrum.

5-Chloro-2-hydrazinobenzoic acid, used in the synthetical work, was obtained in moderate yield from 5-chloroanthranilic acid by the general procedure of Pfannsteil and Janecke,[10] together with an unidentified nitrogenous product which was converted into *m*-chlorobenzoic acid by aqueous sodium hydroxide. 5-Chloro-2-hydrazinobenzoic acid readily gave 5-chloro-3-indazolone (XIX) when boiled with dilute aqueous hydrochloric acid.

Experimental

Reaction of 6-Chloro-4-hydroxycinnoline-3-carboxylic Acid with Pyridine and Acetic Anhydride.—6-Chloro-4-hydroxycinnoline-3-carboxylic acid (10 g.), pyridine (45 ml.), and acetic anhydride (65 ml.) were heated together on the steam-bath for 1 hr. The olive-green crystals of *anhydro-(5-acetyl-2-chloro-5 : 13-dihydro-12-hydroxy-13-oxocinnolino[2,3-c]pyrido[1,2-a]imidazolinium hydroxide*) (II; R′ = Cl) (13·8 g., 94%), decomp. >240°, were collected, washed with dry ether, and dried at 80° *in vacuo* (Found: C, 58·8; H, 3·0; N, 12·8. $C_{16}H_{10}O_3N_3Cl$ requires C, 58·65; H, 3·1; N, 12·8%).

Anhydro-6-chloro-4-hydroxy-2-pyridylcinnolinium Hydroxide (VI; R′ = Cl).—A suspension of the anhydride (II; R = Cl) (13·8 g.) in 2N-hydrochloric acid (800 ml.) was heated under reflux for 5 hr., after which the clear, yellow solution was cooled and neutralised to pH 6—7 with solid sodium carbonate. Yellow crystals separated first during the neutralisation, whilst the mixture was acid to Congo Red; at pH 5—7 this changed to a red gum which was slowly converted into a granular yellow solid. The resulting mixture was stirred for 1 hr. at room temperature, then the solid (9·6 g., 88%), m. p. 158—161°, was collected, washed with water, and recrystallised from ethanol, yielding yellow needles (8·0 g.), m. p. 162—163° (after drying at 80°), of *anhydro-6-chloro-4-hydroxy-2-2′-pyridylcinnolinium hydroxide* (VI; R′ = Cl) (Found: C, 60·4; H, 3·1; N, 16·2. $C_{13}H_8ON_3Cl$ requires C, 60·6; H, 3·1; N, 16·3%). The hydrate, m. p. 132—133°, obtained by air-drying, reverted to the anhydrous material after drying at 80°. The compound was sparingly soluble in boiling water and in ether, and easily soluble in cold, dilute mineral acids.

The annexed Table gives analytical figures for the analogue (VI; R = H).

2-(2-Carboxy-4-chlorophenylazo)pyridine (VIII).—2% Aqueous potassium permanganate (450 ml.) was added during 1 hr. to a vigorously stirred suspension of compound (VI; R′ = Cl) (3 g.) in water (200 ml.) at 40—45°. The mixture was stirred for a further ½ hr. at 40—45°, the excess of permanganate was removed by addition of ethanol, and the mixture was filtered. Acidification of the orange-yellow filtrate to pH 3·8—4·2 with hydrochloric acid gave almost pure 2-(2-carboxy-4-chlorophenylazo)pyridine (VIII) (2·3 g.), m. p. 190—192°, which separated from aqueous ethanol in orange-red needles, m. p. 192—193° (Found: C, 54·9; H, 3·2; N, 16·0.

[10] Pfannsteil and Janecke, *Ber.*, 1942, **75**, 1104.

Analytical values found (a) by Schofield and Simpson [1] *and (b) in the present work for the base* (VI; R′ = H) *and its salts.*

		Found (%)				Required (%)		
		C	H	N	Formula	C	H	N
Base (VI; R′ = H)	(*a*)	63·75	4·6	17·25	$C_{13}H_9N_3,2H_2O$	64·2	5·35	17·3
					$C_{13}H_9ON_3,H_2O$	64·7	4·6	17·4
	(*b*)	69·7	4·0	18·7	$C_{13}H_9N_3,H_2O$	69·3	4·9	18·6
					$C_{13}H_9ON_3$	69·9	4·05	18·8
Hydrochloride ...	(*a*)	57·3	4·15	15·55	$C_{13}H_9N_3,HCl,2H_2O$	55·8	5·0	15·0
					$C_{13}H_9ON_3,HCl,H_2O$	56·2	4·35	15·1
Picrate	(*a*)	51·75	2·75	18·85	$C_{13}H_9N_3,C_6H_3O_7N_3$	5·23	2·8	19·3
	(*b*)	50·3	2·7	—	$C_{13}H_9ON_3,C_6H_3O_7N_3$	50·45	2·7	18·6
		50·7	2·6	—				
Styphnate	(*a*)	48·3	2·45	18·85	$C_{13}H_9N_3,C_6H_3O_8N_3,H_2O$	48·5	3·0	17·9
					$C_{13}H_9ON_3,C_6H_3O_8N_3$	48·7	2·6	17·95

Calc. for $C_{13}H_8O_2N_3Cl$: C, 55·1; H, 3·1; N, 16·05%). Schofield and Simpson's sample [1] (Found: C, 54·95; H, 3·0; N, 16·05%) prepared by the action of hydrochloric acid on 2-*o*-carboxyphenylazopyridine (described by them as a $C_{12}H_9O_4N_3$ acid, m. p. 194—195°), and a mixture of the two samples also had m. p. 192—193°. The infrared absorption spectra of the two samples were identical.

2-o-*Carboxyphenylazopyridine* (VII).—*o*-Nitrosobenzoic acid [11] (15·9 g., 0·105 mole), 2-aminopyridine (9·4 g., 0·1 mole), and 50% aqueous sodium hydroxide (94 ml.) were vigorously stirred at 85—90° for 5 hr., after which water (125 ml.) was added. The mixture was stirred for a further ½ hr. at 80—85°, then cooled and filtered. The solid residue was dissolved in warm water (250 ml.), and the warm filtered solution was acidified with acetic acid, yielding 2-*o*-carboxyphenylazopyridine (11·45 g., 51%), which separated from ethyl acetate in orange-red prisms, m. p. 144—145° (Found: C, 63·3; H, 4·0; N, 18·1%. Calc. for $C_{12}H_9O_2N_3$: C, 63·45; H, 4·0; N, 18·5%). A sample prepared by the method described by Schofield and Simpson [1] (referred to *in their paper* as substance XIV, m. p. 146—147°), and a mixture of the two samples also had m. p. 144—145°. The infrared absorption spectra of the two samples were identical, and both samples gave the same picrate, m. p. 173—174° (Found: C, 47·3; H, 2·6; N, 18·5. Calc. for $C_{12}H_9O_2N_3,C_6H_3O_7N_3$: C, 47·4; H, 2·65; N, 18·4%).

Acidification of the alkaline mother-liquors gave a red-brown solid (4·9 g.), m. p. 233—235°, which on recrystallisation from ethyl acetate and ethanol gave pale-yellow prisms (0·84 g.), m. p. 253—255° (decomp.), of azoxybenzene-2 : 2′-dicarboxylic acid (Found: C, 59·0; H, 3·6; N, 9·9. Calc. for $C_{14}H_{10}O_5N_2$: C, 58·75; H, 3·5; N, 9·8%).

5-*Chloro*-2-*hydrazinobenzoic Acid*.—A stirred suspension of 5-chloroanthranilic acid (57 g., 0·31 mole), water (300 ml.), and concentrated hydrochloric acid (340 ml.) was diazotised at 0—3° with sodium nitrite (21·6 g., 0·3 mole) in water (200 ml.), then added in 30 min. to water (2400 ml.) saturated with sulphur dioxide at 0—5°. During the addition sulphur dioxide was bubbled through the mixture, and the temperature was kept at 5—10°. The mixture was left at room temperature overnight, then filtered (residue A). Addition of concentrated hydrochloric acid (3 l.) to the ice-cooled filtrate gave a colourless precipitate of a hydrochloride, m. p. 197° (decomp.), which yielded 5-*chloro*-2-*hydrazinobenzoic acid* (25 g.) (44%), m. p. 230—235° (decomp.), when stirred with aqueous sodium acetate. Recrystallisation from aqueous 2-ethoxyethanol gave almost colourless needles of the pure product (16·1 g.), m. p. (variable with rate of heating) 265° (decomp.; sintered at 160—180°) (Found: C, 45·2; H, 3·8; N, 14·9. $C_7H_7O_2N_2Cl$ requires C, 45·1; H, 3·8; N, 15·0%) The *benzylidene derivative*, which rapidly separated when benzaldehyde was added to a solution of the crude or recrystallised product in acetic acid, separated from ethanol in yellow prismatic needles, m. p. 249—250° (decomp.) (Found: C, 60·9; H, 3·8; N, 10·4. $C_{14}H_{11}O_2N_2Cl$ requires C, 61·2; H, 4·0; N, 10·2%).

The residue A (33 g.), m. p. 160° (decomp.), reduced warm Fehling's solution and was recovered unchanged after treatment with aqueous sodium acetate. Rapid recrystallisation from aqueous ethanol gave colourless needles of a substance, m. p. 160° (decomp.) (Found: C, 41·7; H, 2·5; N, 7·2; S, 7·0%). A solution of this (1 g.) in 3N-sodium hydroxide (5 ml.) was heated under reflux for 15 min. Acidification then gave *m*-chlorobenzoic acid (0·55 g.), needles (from water), m. p. and mixed m. p. 154—155°.

5-*Chloroindazolone*.—5-Chloro-2-hydrazinobenzoic acid (2 g.) (recrystallised), water (200 ml.),

[11] Bamberger and Pyman, *Ber.*, 1909, **42**, 2306.

and concentrated hydrochloric acid (5 ml.) were heated under reflux for 1 hr. Pure *5-chloro-indazolone* (1·8 g.), which separated, was collected and recrystallised from acetic acid as colourless needles, m. p. 273—275° (decomp.) (Found: C, 50·3; H, 3·0; N, 16·7. $C_7H_5ON_2Cl$ requires C, 49·9; H, 3·0; N, 16·6%).

5-Chloro-1- and -2-2′-pyridyl-3-indazolone.—Crude 5-chloro-2-hydrazinobenzoic acid (9·15 g., 0·048 mole), 2-chloropyridine (5 g., 0·044 mole), and ethanol (40 ml.) were heated at 170—180° for 5 hr. The crystals (0·9 g.) which separated on cooling were collected (mother-liquor A) and dissolved in boiling water (25 ml.) containing sufficient sodium hydroxide to give alkalinity to Clayton Yellow paper. Acidification of the hot solution with acetic acid gave a colourless precipitate of 5-chloro-2-2′-pyridyl-3-indazolone (0·32 g.) (IX), which separated from acetic acid in pale-yellow prisms, m. p. 251—252° (Found: C, 58·7; H, 3·3; N, 17·2. Calc. for $C_{12}H_8ON_3Cl$: C, 58·65; H, 3·3; N, 17·1%). A sample prepared by the method described by Schofield and Simpson,[1] and a mixture of the two samples, also had m. p. 251—252° (Schofield and Simpson [1] give m. p. 253—254° and C, 58·05; H, 3·25; N, 17·6%). Infrared analysis (Nujol mull) showed the absence of a broad band in the 2500—2700 cm.$^{-1}$ region and the presence of strong bands at 3120 and 1660 cm.$^{-1}$. Ultraviolet absorption in methanol (1 mg. per 100 ml.): $\lambda_{max.}$ 254, 292, 298, 340—345 mμ (log ε 4·17, 4·15, 4·14, 3·61). An identical indazolone was produced when an ethanolic solution of 2-(2-carboxy-5-chlorophenylhydrazino)pyridine hydrochloride was heated at 170—180° as described below for preparation of 2-2′-pyridyl-3-indazolone.

The alcoholic mother-liquor A was treated with water (60 ml.), and the solid (3·6 g.), m. p. 209—211°, which separated, was collected. Recrystallisation from acetic acid and then from ethanol afforded pale fawn needles of *5-chloro-1-2′-pyridyl-3-indazolone* (1·1 g.), m. p. 251—252° (Found: C, 59·3; H, 3·4; N, 17·2%) (a mixture of this with the 2-isomer had m. p. 218—220°), $\nu_{max.}$ (Nujol mull) 2500—2700, 1600 w cm.$^{-1}$, $\lambda_{max.}$ (in methanol; 1 mg. per 100 ml.) 260, 337 mμ (log ε 4·32, 4·14). The infrared and ultraviolet data indicate that the 1-isomer exists mainly in the enol form, and the 2-isomer in the keto-form.

Methylation of 5-Chloro-2-2′-pyridyl-3-indazolone.—A solution of the indazolone (0·1 g.) in hot 0·5N-potassium hydroxide (5 ml.) was cooled rapidly to 50°, then shaken with dimethyl sulphate (0·06 ml.) for 10 min. at 45—50°. The solid (0·06 g.), m. p. 125—126°, which separated, was isolated by ether-extraction and recrystallised from aqueous methanol, affording colourless prismatic needles of *5-chloro-1 : 3-dihydro-1-methyl-3-oxo-2-2′-pyridylindazole*, m. p. 123—124° (Found: C, 60·2; H, 3·9%; *M*, 249. $C_{13}H_{10}ON_3Cl$ requires C, 60·1; H, 3·9%; *M*, 260).

2-o-Carboxyphenylhydrazinopyridine.—(*a*) 2-*o*-Carboxyphenylazopyridine (2·27 g., 0·01 mole) in ethanol (100 ml.) was shaken with hydrogen at room temperature pressure in the presence of palladium oxide. Absorption of hydrogen (1 mol.) ceased after ~1 hr. The solid, which separated, was collected and digested with cold 0·5N-sodium hydroxide (30 ml.). Acidification of the filtered digests with acetic acid gave the crude *hydrazine* (2·05 g.), m. p. 220° (decomp.), which separated from 2-ethoxyethanol in almost colourless needles, m. p. 232° (decomp.) (Found: C, 62·7; H, 4·8; N, 18·2. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·85; N, 18·3%). The *hydrochloride* separated when a hot solution of the base (1 g.) in water (10 ml.) and concentrated hydrochloric acid (2 ml.) was cooled; recrystallisation from methanol–ether afforded needles, m. p. 243—244° (decomp.) (Found: C, 54·4; H, 4·8; N, 15·5. $C_{12}H_{11}O_2N_3$,HCl requires C, 54·3; H, 4·6; N, 15·8%).

(*b*) A solution of 2-*o*-carboxyphenylazopyridine (2·27 g., 0·01 mole) in chloroform (25 ml.) was treated dropwise with thiophenol (1·13 ml., 0·011 mole) at 20—22°, then set aside at room temperature for 2 days. The solid (1·84 g.), m. p. 215° (decomp.), was collected and recrystallised from 2-ethoxyethanol, yielding fawn needles of the hydrazine, identical with a sample described in (*a*). Similar results were obtained by using ethanethiol.

2-(2-Carboxy-4-chlorophenylhydrazino)pyridine.—Prepared by methods (*a*) and (*b*), this *compound* separated from 2-ethoxyethanol in almost colourless needles, m. p. 252—253° (decomp.) (Found: C, 54·6; H, 3·7; N, 15·5. $C_{12}H_{10}O_2N_3Cl$ requires C, 54·6; H, 3·8; N, 15·9%).

2-2′-Pyridyl-3-indazolone (XVIII).—2-*o*-Carboxyphenylhydrazinopyridine hydrochloride (2 g.) and ethanol (20 ml.) were heated at 170—180° for 5 hr. The *indazolone* (0·75 g.), m. p. 185—186°, separated on cooling, and a further crop (0·3 g.), m. p. 176—178°, was obtained by addition of water to the mother-liquors. Recrystallisation from ethanol containing a trace of aqueous sodium hydrogen carbonate gave pale-yellow prismatic needles, m. p. 186—187°. A sample prepared by alkaline degradation of compound (V) by Schofield and Simpson's procedure,[1] and a mixture of the two, had m. p. 186—187° (Found: C, 68·1; H, 4·4; N, 19·8.

Calc. for $C_{12}H_9ON_3$: C, 68·2; H, 4·3; N, 19·9%). Infrared analysis (in Nujol) showed the absence of a broad band at 2500—2700 cm.$^{-1}$ and the presence of strong bands at 3180 and 1655 cm.$^{-1}$, indicating, as with the 5-chloro-derivative, that the compound exists mainly in the enol form.

1-2′-*Pyridyl*-3-*indazolone*.—*o*-Hydrazinobenzoic acid (7·4 g.), 2-chloropyridine (5 g.), and ethanol (40 ml.) were heated together at 170—180° for 5 hr. The cooled product was treated with water (80 ml.), yielding crystals of 1-2′-*pyridyl*-3-*indazolone* (1·21 g.), pale-yellow needles (from methanol), m. p. 204—205° (Found: C, 68·6; H, 4·4; N, 19·9. $C_{12}H_9ON_3$ requires C, 68·2; H, 4·3; N, 19·9%), broad band (Nujol mull) between 2500 and 2700 cm.$^{-1}$, weak band at 1660 cm.$^{-1}$, $\lambda_{max.}$ (in methanol) (1 mg. per 100 ml.) 255 mμ (log ε 4·32, 4·25).

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452. *Acyl Isothiocyanates. Part III.*[1] *Properties of Some Phosphoroisothiocyanatidates.*

By D. T. ELMORE and J. R. OGLE.

Diphenyl phosphoroisothiocyanatidate affords good yields of addition products with amines, methanol, and methanethiol. Some *N*-diphenoxyphosphinylthioureas are remarkably sensitive to hydrolysis, and possible mechanisms are considered. Addition and substitution are competitive when amines react with diethyl phosphoroisothiocyanatidate, but the controlling factors have not been satisfactorily elucidated. Attempts to prepare dibenzyl phosphoroisothiocyanatidate and its derivatives are described.

EARLIER papers in this series[1,2] have described some of the chemistry of simple acyl isothiocyanates. Depending on various conditions mentioned therein, reaction of these compounds with nucleophiles may occur in either of two ways; addition to the isothiocyanate group affords *N*-acylthiocarbamoyl compounds, whereas substitution at the carbonyl-carbon atom gives *N*-acyl derivatives. In the present paper, we record some experiments with phosphorus-containing isothiocyanates. Phosphorous and phosphoric tri-isothiocyanates were the subject of early studies by Miquel and by Dixon,[3] but interest in isothiocyanates of phosphorus has revived only in the last decade with the synthesis of esters (I) of phosphoroisothiocyanatidic acid. The diethyl ester (I; R = Et) was the first compound of this type to be prepared,[4,5] but the reported properties were not consistent. This discrepancy has been resolved by more recent studies,[6,7] as well as by the present work. The diphenyl ester (I; R = Ph) was prepared by Kenner, Khorana, and Stedman,[8] and several other aryl derivatives are now known.[6,7] Phosphoroisothiocyanatidates have commonly been prepared by treatment of phosphorochloridates in a suitable solvent with potassium thiocyanate,[4,5,7,8] and the latter also reacts with tetraphenyl pyrophosphate to give diphenyl phosphoroisothiocyanatidate.[8] Michalski and Wieczorkowski [6] have recently

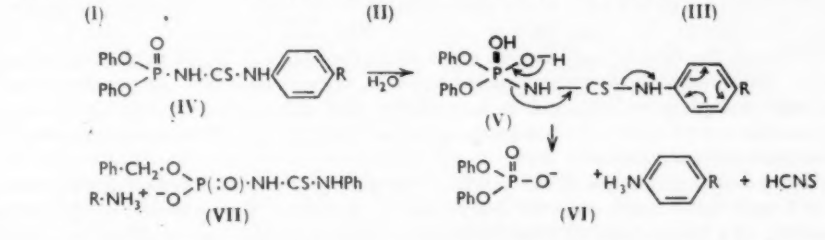
[1] Part II, Elmore and Ogle, *J.*, 1958, 1141.
[2] Elmore, Ogle, Fletcher, and Toseland, *J.*, 1956, 4458.
[3] Miquel, *Ann. Chim. Phys.*, 1877, **11**, 341; Dixon, *J.*, 1901, **79**, 541; Dixon and Taylor, *J.*, 1908, **93**, 2148; Dixon, *J.*, 1904, **85**, 350.
[4] Saunders, Stacey, Wild, and Wilding, *J.*, 1948, 699.
[5] Cook, Ilett, Saunders, Stacey, Watson, Wilding, and Woodcock, *J.*, 1949, 2921.
[6] Michalski and Wieczorkowski, *Roczniki Chem.*, 1955, **29**, 137; 1957, **31**, 585.
[7] Leuchenko and Zhmurova, *Ukrain. khim. Zhur.*, 1956, **22**, 623.
[8] Kenner, Khorana, and Stedman, *J.*, 1953, 673.

devised a novel synthesis, which involves the oxidation of dialkyl phosphites with thiocyanogen; this recalls the preparation of phosphorochloridates by chlorination of phosphite diesters.[9]

Phosphoroisothiocyanatidates have been reported to react additively with amines [6,7,8] and alcohols.[10] We have found that diphenyl phosphoroisothiocyanatidate in inert solvents reacts additively with a variety of amines to give the corresponding thioureas (II) in good yield. Since diphenyl phosphoroisothiocyanatidate in aqueous dioxan at pH 8·5 was hydrolysed completely within 5 min., experiments, similar to those between benzoyl isothiocyanate and amino-acids in aqueous solution,[1] were precluded. The consumption of 2 moles of alkali per mole of isothiocyanatidate at constant pH, however, indicated that hydrolysis comprised only a nucleophilic attack at the phosphorus atom, in contrast to the behaviour of benzoyl isothiocyanate.[1] It thus appears that diphenyl phosphoroisothiocyanatidate is intermediate in properties between aliphatic and aromatic acyl isothiocyanates.

Methanol and methanethiol afforded the expected thioncarbamate (III; R = Ph, X = O) and dithiocarbamate (III; R = Ph, X = S) respectively. The latter was of interest as a potential reagent for procuring the stepwise degradation of peptides from the *N*-terminus.[2,11] It reacted rapidly with glycine ethyl ester in ethanol to give *N*-diphenoxyphosphinylthiocarbamoylglycine ethyl ester (II; R = Ph, R′ = $CH_2{\cdot}CO_2Et$, R″ = H), identical with a sample prepared directly from the phosphoroisothiocyanatidate and glycine ethyl ester. Similar reactions with glycylglycine ethyl ester afforded only intractable gums, which appeared to contain the expected product, but could not be purified. Hot, dilute acids degraded the glycine derivative (II; R = Ph, R′ = $CH_2{\cdot}CO_2Et$, R″ = H) to 2-thiohydantoin in low yield, while the gummy product from the peptide ester broke down in acids in a complex manner, and only traces of 2-thiohydantoin were detected. A possible explanation of these observations lies in the peculiar lability to hydrolysis of the *N*-diphenoxyphosphinyl group in certain thioureas discussed below. These results, together with the insolubility of the dithiocarbamate, discouraged us from further examination of its possible use as a reagent in the stepwise degradation of peptides.

We were surprised to find that *N*-aryl-*N*′-diphenoxyphosphinylthioureas were extremely readily hydrolysed. For example, *p*-(*N*-diphenoxyphosphinylthiocarbamoyl)-aminobenzoic acid (IV; R = *p*-CO_2H) or its ethyl ester, which were obtained by reaction of diphenyl phosphoroisothiocyanatidate and *p*-aminobenzoic acid in dry ether or ethyl



p-aminobenzoate in dry acetonitrile, was quantitatively and rapidly converted into *p*-carboxyanilinium or *p*-ethoxycarbonylanilinium diphenyl phosphate during attempted recrystallisation from aqueous ethanol. *N*-Diphenoxyphosphinyl-*N*′-phenylthiourea survived this treatment, but was hydrolysed to anilinium diphenyl phosphate after 8 hr. in

[9] McCombie, Saunders, and Stacey, *J.*, 1945, **380**; Atherton, Openshaw, and Todd, *ibid.*, p. 382.
[10] Zhmurova, *Ukrain. khim. Zhur.*, 1956, **22**, 627.
[11] Elmore and Toseland, *J.*, 1954, 4533.

refluxing water. In contrast, *p*-(*N*-benzoylthiocarbamoyl)aminobenzoic acid and *N*-cyclohexyl-*N'*-diphenoxyphosphinylthiourea were stable under these conditions. It appears from these results that the diphenoxyphosphinyl group has some characteristic, not possessed by the benzoyl group, which promotes lability to hydrolysis. An electron-attracting group at the other end of the molecule also appears to be necessary. In addition to the above products, thiocyanate ion (approximately 0·9 equivalent) was found in the hydrolysate of the thiourea (IV; R = CO_2Et). Hydrogen sulphide, an expected breakdown product of thiocyanic acid, was also usually evolved. Several reaction mechanisms are possible, and these may occur concurrently, especially since the pH drops during reaction. Hydrolysis of the thioureas (II; R = Ph, R' = aryl, R'' = H) may occur at *a*, *b*, or *c*. While we cannot be certain of the mechanism in absence of a kinetic investigation, we propose that, by using the *d*-orbitals of phosphorus, a molecule of water is added, and this step is followed by a synchronous cleavage at both *a* and *c*, as recently suggested by Grob [12] to explain the cleavage of certain γ-aminoalkyl halides. A synchronous mechanism is preferred, since the $\rangle N{\cdot}CS{\cdot}N\langle$ system is planar. The mechanism also requires the simultaneous action of electron-donating and electron-attracting groups at opposite ends of the molecule. The tendency of the intermediate (V) to lose a proton might provide the former, while the latter influence could be derived from the electromeric effects of the aromatic ring. Replacement of this by the electron-donating cyclohexyl group would explain the stability of *N*-cyclohexyl-*N'*-diphenoxyphosphinylthiourea. This mechanism accounts for the formation of thiocyanate ion and diphenyl phosphate. It appears that inductive electron-withdrawal is also effective, since *N*-diphenoxyphosphinylthiocarbamoylsarcosine *p*-toluidide (II; R = Ph, R' = Me, R'' = $CH_2{\cdot}CO{\cdot}NH{\cdot}C_6H_4Me$-*p*) was completely hydrolysed by boiling aqueous dioxan in 15 min. It is worth noting that *N*-diphenoxyphosphinylthiocarbamoyl derivatives of amino-acids, if they were readily available, would be useful compounds for peptide synthesis, since the protecting group could be removed under very mild conditions. A number of simple *N*-acylthiocarbamoylamino-acids have been converted into amides by standard procedures for peptide synthesis.[13]

Nucleophilic attack by a water molecule at the phosphorus atom of the *N*-diphenoxyphosphinylthioureas (IV) could result in cleavage of the P–N bond and lead to diphenyl phosphate and a thiourea, which might be further hydrolysed under the acidic conditions. For example, we found that after equimolar quantities of diphenyl phosphate and *N*-phenylthiourea had been heated in refluxing water for 8 hr., only 30% of the thiourea could be recovered; in addition, anilinium diphenyl phosphate (23%) was isolated and thiocyanate ions were present in solution. Since, under similar conditions, *N*-diphenoxyphosphinyl-*N'*-phenylthiourea afforded 84% of the theoretical yield of anilinium diphenyl phosphate, the above mechanism can make only a minor contribution. Nucleophilic attack of water molecules at the thiocarbonyl-carbon atom could theoretically result in cleavage at either *b* or *c*. Both mechanisms are considered unlikely, since in each case one product would be diphenyl phosphoramidate, and it is unlikely that this would be hydrolysed to any appreciable extent under the conditions of hydrolysis of, *e.g.*, *p*-(*N*-diphenoxyphosphinylthiocarbamoyl)aminobenzoic acid.

The physical properties of our sample of diethyl phosphoroisothiocyanatidate were in accord with those most recently described.[6,7] Moreover, the presence in the infrared spectrum of a broad band at 1980—2050 $cm.^{-1}$ with a shoulder at *ca.* 2070 $cm.^{-1}$, similar to those observed for alkyl isothiocyanates, diphenyl phosphoroisothiocyanatidate, and benzoyl isothiocyanate,[14] reinforces the conclusion of Michalski and Wieczorkowski,[6] based on molar refractivity measurements, that the compound is an isothiocyanate rather than a

[12] Grob, *Helv. Chim. Acta*, 1955, **38**, 594; *Experientia*, 1957, **13**, 126; Kekulé Symp. Theor. Org. Chem., London, Butterworths, 1958.
[13] Elmore and Toseland, *J.*, 1957, 2460.
[14] Lieber, Rao, and Ramachandran, *Spectrochim. Acta*, 1959, **13**, 296; Elmore and Ogle, unpublished observations.

thiocyanate. We attribute the low frequency of the isothiocyanate band to conjugation with the P=O group. Although diethyl phosphoroisothiocyanatidate afforded crystalline thioureas after reaction with a variety of amines, yields were usually less than 50% of theoretical, and we believe that nucleophilic substitution at the phosphorus atom competes strongly with addition at the isothiocyanate group. In order to gain insight into the factors controlling the relative rates of the competing reactions, we allowed the phosphoroisothiocyanatidate in benzene or acetonitrile to react with aniline, ethylamine, cyclohexylamine, and t-butylamine under standard conditions and determined the ratio of thiourea to thiocyanate ion formed. The results were disappointing, since, although we could usually account for 100 ± 5% of reactant used, yields were rather variable under a particular set of conditions and not very sensitive to change of base or solvent.

[*Note Added, April 27th*, 1959.—Very recently, Kulka (*Canad. J. Chem.*, 1959, **37**, 525) has reported that diethyl phosphoroisothiocyanatidate is readily decomposed to ethyl thiocyanate. The physical properties of our preparation agree closely with those recorded by Kulka, but it is possible that our sample had partially decomposed on storage. This would explain, to some extent, the low yields of addition products with amines and would mask effects due to change of base and solvent.]

The preparation of dibenzyl phosphoroisothiocyanatidate, as expected, presented considerable difficulty. The ready monodebenzylation of dibenzyl phosphorochloridate by tertiary bases has already been observed,[15] and our own experience in the synthesis of benzyloxycarbonyl isothiocyanate [8] confirmed earlier reports [16] on the ease with which benzyl esters are attacked by thiocyanate ions. Accordingly, reaction between potassium thiocyanate and dibenzyl phosphorochloridate was conducted in a mixture of carbon tetrachloride and acetonitrile at ~−20°, but the rate of formation of isothiocyanatidate appeared to be inconveniently slow. Oxidation of dibenzyl phosphite with thiocyanogen seemed a more attractive approach, but numerous experiments revealed its capriciousness. No attempt was made to isolate the phosphoroisothiocyanatidate, and addition of aniline consistently afforded the *O*-benzyl-*N*-phenylthiocarbamoylphosphoramidic acid [isolated as its cyclohexylammonium (VII; R = C_6H_{11}) or anilinium (VII; R = Ph) salts] in 10—15% yield. Presumably, monodebenzylation was effected by thiocyanate ions. After oxidation of dibenzyl phosphite at −10°, *N*-dibenzyloxyphosphinyl-*N'*-phenylthiourea (II; R = Ph·CH_2, R' = Ph, R'' = H) was isolated. Several experiments using cyclohexylamine and methanethiol gave no crystalline addition products.

Experimental

Diphenyl phosphoroisothiocyanatidate (I; R = Ph) was prepared by a modification of the method of Kenner *et al.*;[8] the volume of acetonitrile was reduced to one-fifth of that previously used. The mixture was heated under reflux for 30 min., cooled to 0°, and filtered without addition of benzene. After removal of solvent, the product was purified by distillation at 0·01 mm. (bath-temp. 210—230°) or by short-path distillation at 130—140°/0·001 mm., then having n_D 1·5840. The isothiocyanate group gave rise to a broad peak at 1970—2040 cm.$^{-1}$ with a shoulder at *ca.* 2120 cm.$^{-1}$ in the infrared spectrum.

Methyl N-*Diphenoxyphosphinylthioncarbamate* (III; R = Ph, X = O).—Diphenyl phosphoroisothiocyanatidate (1 g.) was heated in methanol (5 c.c.) for 2 hr. Evaporation of solvent under reduced pressure afforded the hygroscopic thioncarbamate (0·9 g.), which had m. p. 129—130° after recrystallisation from ethyl acetate–light petroleum (b. p. 40—60°) (Found: C, 52·2; H, 4·4; N, 4·6; P, 10·1; S, 9·6. Calc. for $C_{14}H_{14}O_4NSP$: C, 52·0; H, 4·4; N, 4·3; P, 9·6; S, 9·9%). Zhmurova [10] records m. p. 132—134°.

Methyl N-*Diphenoxyphosphinyldithiocarbamate* (III; R = Ph, X = S).—(*a*) Diphenyl phosphoroisothiocyanatidate (7·25 g.) and methanethiol (5 g.) were kept in acetonitrile (50 c.c.) for 5 days at room temperature. The *dithiocarbamate*, which separated when the mixture was

[15] Atherton, Howard, and Todd, *J.*, 1948, 1106; Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815; Clark and Todd, *J.*, 1950, 2023.
[16] Morrison and Atherton, B.P., 675, 779.

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poured into a large volume of water, was recrystallised from ethyl acetate–light petroleum (b. p. 40—60°) and then had m. p. 133—134° (Found: C, 50·0; H, 4·2; P, 9·6. $C_{14}H_{14}O_3NS_2P$ requires C, 49·6; H, 4·2; P, 9·2%).

(*b*) Diphenyl phosphorochloridate (13·4 g.) and potassium thiocyanate (5·0 g.) were heated in acetonitrile (50 c.c.) for 30 min. After cooling, methanethiol (5 g.) was added and the solution was kept for 5 days at room temperature. Isolation as before afforded the product (8·5 g.) with identical m. p.

N-Diphenoxyphosphinyl-N′-phenylthiourea (IV; R = H).—This was prepared as described by Leuchenko and Zhmurova,[7] and by a method similar to (*b*) for the dithiocarbamate above. Recrystallised from aqueous ethanol it had m. p. 144—145°, whereas Leuchenko and Zhmurova [7] record m. p. 143—144° (Found: C, 59·5; H, 4·9; N, 7·5; P, 7·9; S, 8·4. Calc. for $C_{19}H_{17}O_3N_2SP$: C, 59·4; H, 4·5; N, 7·3; P, 8·1; S, 8·4%). The thiourea (0·2 g.) gradually dissolved in refluxing water (10 c.c.) during 8 hr. On cooling, anilinium diphenyl phosphate (0·15 g.) separated and had m. p. 165·5—166·5°, undepressed on admixture with synthetic material.

Hydrolysis of N-Phenylthiourea.—*N*-Phenylthiourea (0·152 g.) and diphenyl phosphate (0·25 g.) were heated in water (10 c.c.) under reflux for 8 hr. On cooling, anilinium diphenyl phosphate (0·08 g.) crystallised, and had m. p. and mixed m. p. 164—165° after recrystallisation from water. *N*-Phenylthiourea (0·045 g.) was recovered from the mother-liquors.

N-Diphenoxyphosphinyl-N′-p-nitrophenylthiourea (IV; R = NO_2).—This *compound* (2·82 g.) was obtained by interaction of diphenyl phosphoroisothiocyanatidate (2·91 g.) and *p*-nitroaniline (1·38 g.) in benzene (10 c.c.). Recrystallised first from ethyl acetate and then from benzene–light petroleum (b. p. 40—60°), it had m. p. 139—140° (Found: C, 53·2; H, 4·0; N, 9·7; P, 6·7; S, 7·4. $C_{19}H_{16}O_5N_3SP$ requires C, 53·2; H, 3·8; N, 9·8; P, 7·2; S, 7·5%). The thiourea (0·25 g.) was heated under reflux in water for 14 hr. The cooled solution deposited *p*-nitroaniline (0·09 g.), which had m. p. 144—145° alone and in admixture with an authentic sample after recrystallisation from aqueous ethanol. The hydrolysis mother-liquors were strongly acidified and extracted with 4 portions of ethyl acetate. The combined extracts were dried (Na_2SO_4) and evaporated to a gum which was dissolved in benzene. Addition of cyclohexylamine caused cyclohexylammonium diphenyl phosphate to separate in quantitative yield. Recrystallised from ethanol–ether, it had m. p. and mixed m. p. 195·5—196·5°.

p-(*N-Diphenoxyphosphinylthiocarbamoyl*)*aminobenzoic Acid* (IV; R = CO_2H).—Diphenyl phosphoroisothiocyanatidate (2·91 g.) and *p*-aminobenzoic acid (1·37 g.) were kept overnight in ether (300 c.c.). An insoluble material was removed, and the solution was concentrated under reduced pressure to 50 c.c. Addition of light petroleum (b. p. 40—60°) precipitated a gum. Further addition of light petroleum (b. p. 40—60°) to the supernatant liquid and storage at 0° afforded the *thiourea* (1·22 g., 1·71 g., and 2·85 g. in successive experiments); it had m. p. 128—130° and could not be recrystallised owing to its ready decomposition (Found: C, 56·0; H, 4·3; N, 6·9; P, 7·1; S, 7·6. $C_{20}H_{17}O_5N_2SP$ requires C, 56·1; H, 4·0; N, 6·5; P, 7·2; S, 7·5%). The thiourea (0·10 g.) was heated in 50% aqueous ethanol (10 c.c.) under reflux for 15 min. Solvent was removed and the residue of p-*carboxyanilinium diphenyl phosphate* was crystallised from aqueous ethanol. It had m. p. 188—189°, undepressed by admixture with a sample obtained by interaction of *p*-aminobenzoic acid and diphenyl phosphate in dioxan; the two specimens had identical infrared spectra (Found: C, 58·0; H, 4·7; N, 3·6; P, 7·6. $C_{19}H_{18}O_6NP,\frac{1}{2}H_2O$ requires C, 57·6; H, 4·8; N, 3·5; P, 7·8%).

Ethyl p-(*N-Diphenoxyphosphinylthiocarbamoyl*)*aminobenzoate* (IV; R = CO_2Et).—Diphenyl phosphoroisothiocyanatidate (5·82 g.) and ethyl *p*-aminobenzoate (3·36 g.) were kept for 6 hr. in acetonitrile (25 c.c.). The *product* (8·36 g.) separated and was recrystallised from ethyl acetate–light petroleum (b. p. 40—60°); it then had m. p. 126—127° (Found: C, 57·8; H, 4·9; N, 5·6; P, 6·6; S, 7·2. $C_{22}H_{21}O_5N_2SP$ requires C, 57·9; H, 4·6; N, 6·1; P, 6·8; S, 7·0%). Heated in boiling water, this compound (1 g.) dissolved within 20 min., and hydrogen sulphide was evolved. [A separate experiment carried out in dioxan–water (3 : 2) at 100° revealed that approximately 90% of the theoretical amount of thiocyanate ion was liberated within 3 min.] On cooling, a gum separated and was extracted with two portions of ethyl acetate. The combined extracts were dried (Na_2SO_4), evaporated, and treated with light petroleum (b. p. 40—60°). The resulting gum (0·80 g.) solidified at 0° and was recrystallised from aqueous ethanol. The p-*ethoxycarbonylanilinium diphenyl phosphate* had m. p. 98—99°, undepressed by admixture with a sample prepared from ethyl *p*-aminobenzoate and diphenyl phosphate in

benzene; the two specimens had identical spectra (Found: C, 60·6; H, 5·4; N, 3·7. $C_{21}H_{22}O_6NP$ requires C, 60·7; H, 5·3; N, 3·4%).

N-Diphenoxyphosphinylthiocarbamoylsarcosine p-Toluidide (II; R = Ph, R′ = Me, R″ = CH_2·CO·NH·C_6H_4·Me-*p*).—Sarcosine *p*-toluidide (from 2·59 g. of hydrobromide[17]) and diphenyl phosphoroisothiocyanatidate (2·91 g.) in benzene (20 c.c.) afforded this *compound* (4·5 g.). Recrystallised from ethanol–ethyl acetate and then from ethanol, it had m. p. 141·5—142·0° (Found: C, 58·4; H, 5·3; N, 8·6; P, 6·9; S, 7·2. $C_{23}H_{24}O_4N_2SP$ requires C, 58·8; H, 5·2; N, 9·0; P, 6·6; S, 6·8%). A solution of this compound in dioxan–water (3 : 2) was heated for 15 min. and then evaporated under reduced pressure to a gum. This was separated into basic and acidic fractions by standard methods, and afforded sarcosine *p*-toluidide [61%; isolated as the hydrobromide,[17] m. p. 258—260° (decomp.)] and diphenyl phosphate (75%; isolated as its cyclohexylammonium salt, m. p. and mixed m. p. 195—196°).

N-Diphenoxyphosphinylthiocarbamoylsarcosine ethyl ester (II; R = Ph, R′ = Me, R″ = CH_2·CO_2Et) was prepared in the same manner as the *p*-toluidide. Recrystallised from benzene–light petroleum (b. p. 40—60°), it had m. p. 124·5—125·5° (Found: C, 52·6; H, 5·4; N, 6·6; S, 7·5. $C_{18}H_{21}O_5N_2SP$ requires C, 52·9; H, 5·2; N, 6·9; S, 7·9%).

N-Diphenoxyphosphinylthiocarbamoylglycine Ethyl Ester (II; R = Ph, R′ = H, R″ = CH_2·CO_2Et).—This *ester* was prepared in the same manner as the sarcosine derivative. Recrystallised from ethyl acetate–light petroleum (b. p. 40—60°), it had m. p. 123—124° (Found: C, 51·9; H, 4·9; N, 7·2; P, 8·4; S, 8·2. $C_{17}H_{19}O_5N_2SP$ requires C, 51·8; H, 4·9; N, 7·1; P, 7·9; S, 8·1%). It was also obtained by keeping a solution of methyl *N*-diphenoxyphosphinyldithiocarbamate (0·75 g.) and glycine ethyl ester (0·25 g.) in ethanol (5 c.c.) overnight. Evaporation of the solvent under reduced pressure gave an oil which crystallised at 0°. Recrystallisation from ethyl acetate–light petroleum (b. p. 40—60°) and then from aqueous ethanol gave a product (0·5 g.), which had m. p. and mixed m. p. 124—125°. The two specimens had identical infrared spectra. This compound (0·3 g.) was heated in 4N-hydrochloric acid (15 c.c.) and ethanol (15 c.c.) for 3·5 hr. After concentration under reduced pressure to 10 c.c. the pH was adjusted to 7·5, and the solution was extracted continuously with ether overnight. Removal of ether afforded 2-thiohydantoin (15 mg.), which was recrystallised from water. It then had m. p. and mixed m. p. 224—226° (decomp.), and was indistinguishable from an authentic specimen on a paper chromatogram irrigated with butan-1-ol saturated with water.

Reaction of diphenyl phosphoroisothiocyanatidate or methyl *N*-diphenoxyphosphinyldithiocarbamate and glycylglycine ethyl ester gave intractable gums. Treatment of these with 90% trifluoroacetic acid or a mixture of water (1 vol.) and acetic acid saturated with hydrogen chloride (9 vols.) gave only traces of 2-thiohydantoin detectable by paper chromatography.

Diethyl Phosphoroisothiocyanatidate (I; R = Et).—This compound was prepared by the methods of Kenner *et al.*[6] (54%) and Michalski and Wieczorkowski[6] (74%) and had b. p. 70—72°/0·6 mm., n_D^{19} 1·4751 (Found: C, 30·8; H, 5·1; N, 7·1; P, 15·1. Calc. for $C_5H_{10}O_3NSP$: C, 30·8; H, 5·2; N, 7·2; P, 15·9%). There was a broad band at 1980—2050 cm.$^{-1}$ with a shoulder at *ca.* 2070 cm.$^{-1}$ in the infrared spectrum.

N-Diethoxyphosphinyl-N′-ethylthiourea (II; R = R′ = Et, R″ = H).—Reaction between equimolar quantities of diethyl phosphoroisothiocyanatidate and ethylamine in benzene or acetonitrile afforded this *thiourea* (0—31%), which crystallised from benzene–light petroleum (b. p. 40—60°). Recrystallised from carbon tetrachloride–light petroleum (b. p. 40—60°), it had m. p. 61—62° (Found: C, 34·9; H, 7·1; N, 11·6; P, 13·1; S, 13·7. $C_7H_{17}O_3N_2SP$ requires C, 35·0; H, 7·1; N, 11·7; P, 12·9; S, 13·4%).

N-Cyclohexyl-N′-diethoxyphosphinylthiourea (II; R = Et, R′ = C_6H_{11}, R″ = H).—This *compound* (34—61%), prepared in a similar manner, crystallised from benzene–light petroleum (b. p. 40—60°). After recrystallisation from light petroleum (b. p. 60—80°), it had m. p. 91—92° (Found: C, 45·0; H, 7·8; P, 10·7. $C_{11}H_{23}O_3N_2SP$ requires C, 44·9; H, 7·9; P, 10·5%).

N-Diethoxyphosphinyl-N′-t-butylthiourea (II; R = Et, R′ = Bu^t, R″ = H).—Similarly prepared to the above compounds, this *thiourea* (15—24%) crystallised from light petroleum (b. p. 90—120°) and had m. p. 108—109° (Found: C, 40·4; H, 7·9; N, 10·4; P, 12·3; S, 12·4. $C_9H_{21}O_3N_2SP$ requires C, 40·3; H, 7·9; N, 10·4; P, 11·6; S, 12·0%).

Dibenzyl Phosphoroisothiocyanatidate (I; R = Ph·CH_2).—A solution of thiocyanogen (0·1 mole) in carbon tetrachloride (250 c.c.) was added during 4 hr. to a well-stirred solution of dibenzyl phosphite (0·075 mole) in carbon tetrachloride (200 c.c.) at a temperature below −10°.

[17] Elmore, unpublished work.

The mixture was kept at 0° for 48 hr., filtered through Hyflo-Supercel, and aerated with a brisk stream of nitrogen for 1 hr. This solution was used without further purification for the experiments described below. Use of 0·4 mole of thiocyanogen or increase of the time of reaction to 96 hr. did not improve yields in the subsequent reactions.

N-Dibenzyloxyphosphinyl-N′-phenylthiourea (II; R = Ph·CH_2, R′ = Ph, R″ = H).—Aniline (2·8 g.), added to an aliquot part (90 c.c.) of the solution of dibenzyl phosphoroisothiocyanatidate prepared as described above, caused a yellow oil to separate immediately. After 3 hr., chloroform (90 c.c.) was added, and the mixture was successively extracted with 2N-hydrochloric acid, saturated sodium hydrogen carbonate and water (twice), and dried (Na_2SO_4). Concentration under reduced pressure to 25 c.c. and addition of light petroleum (b. p. 40—60°) caused the *thiourea* (1·35 g.) to separate. Recrystallised from ethyl acetate–light petroleum (b. p. 40—60°), it had m. p. 107—108° (Found: C, 60·7; H, 5·2; N, 6·9; P, 7·6; S, 8·1. $C_{21}H_{21}O_3N_2SP$ requires C, 61·2; H, 5·1; N, 6·8; P, 7·5; S, 7·8%). Two subsequent experiments gave yields of 0·66 g. and 1·90 g.

O-Benzyl-N-phenylthiocarbamoylphosphoramidic Acid.—The sodium hydrogen carbonate extract obtained in the foregoing experiment was strongly acidified and extracted with 6 portions of ether. To the combined and dried (Na_2SO_4) ether extracts was added an excess of cyclohexylamine. The resultant *cyclohexylammonium O-benzyl-N-phenylthiocarbamoylphosphoramidate* (VII; R = C_6H_{11}) (1·2 g.) was recrystallised first from 95% ethanol and then from 10% ethanol, and had m. p. 151—152° (Found: C, 56·7; H, 6·4; N, 9·8; P, 7·8; S, 8·0. $C_{20}H_{28}O_3N_3SP$ requires C, 57·0; H, 6·7; N, 10·0; P, 7·4; S, 7·6%).

Aniline (5·8 g.) was added to an aliquot part (90 c.c.) of the isothiocyanatidate solution described above, and the mixture was kept overnight at room temperature. The oil (2·65 g.), which initially separated, solidified to a gummy solid and was collected and washed with chloroform. Dissolution in hot chloroform and addition of light petroleum (b. p. 40—60°) afforded *anilinium O-benzyl N-phenylthiocarbamoylphosphoramidate* (VII; R = Ph) (1·5 g.). After recrystallisation first from ethanol–ether–light petroleum (b. p. 40—60°) and then from ethanol–cyclohexane, it had m. p. 138—140° (Found: C, 58·1; H, 5·2; N, 9·8; P, 7·8; S, 8·0. $C_{20}H_{22}O_3N_2SP$ requires C, 57·8; H, 5·3; N, 10·1; P, 7·5; S, 7·7%). It was found impossible to isolate *N*-dibenzyloxyphosphinyl-*N′*-phenylthiourea from the carbon tetrachloride mother-liquors from this preparation.

The authors are grateful to Sir Alexander Todd, F.R.S., for permission to complete this work in his Department, and to Imperial Chemical Industries Ltd. for financial assistance.

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453. *Conformations of the Cyclohexa-1,4-diene Ring System.*

By F. H. Herbstein.

The relative stabilities of various conformations of cyclohexa-1,4-diene, 9,10-dihydroanthracene, and 9,10-dihydro-1,2:5,6-dibenzanthracene (I) have been calculated, account being taken of angle strain and interactions between non-bonded hydrogen atoms. In agreement with experiment, calculations indicated the dihydroanthracene as folded (dihedral angle * ~150°), and the dihydrodibenzanthracene as planar. The calculations for cyclohexa-1,4-diene indicate a folded molecule, in approximate agreement with dipole-moment measurements but not with deductions from infrared and Raman spectroscopy.

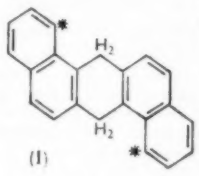
Information regarding the conformation of the cyclohexa-1,4-diene ring is contradictory. Simple considerations [1] based on minimisation of angle strain within the ring suggest that

* In this paper " dihedral angle " is used to specify the angle between the planes containing carbon atoms in positions (*a*) 6,1,2,3 and (*b*) 6,5,4,3 of the cyclohexa-1,4-diene ring.

[1] Beckett and Mulley, *Chem. and Ind.*, 1955, 146.

the molecule should be folded, with symmetry C_{2v} and a dihedral angle of about 141°. Measurements [2] have shown that 1,4-dichlorocyclohexa-1,4-diene has a dipole moment of 0·3 D, from which it has been concluded that the ring is folded but flatter than expected for tetrahedral angles at the methylene groups. On the other hand, Raman and infrared spectra of cyclohexa-1,4-diene itself have been interpreted [3] in terms of a structure deviating only slightly from the rigorous D_{2h} (planar) conformation.

More conclusive evidence should be obtained from crystal-structure analyses, where results are available for two molecules containing the cyclohexa-1,4-diene ring. The structure of 9,10-dihydroanthracene was determined [4] from two-dimensional projections down [010] and [100]. It was folded about the axis through the methylene-carbon atoms, with a dihedral angle of 145°. The measured dipole moment of 0·4 D shows that the molecule is also folded in solution.[5] On the other hand crystallographic data [6,7] show that 9,10-dihydro-1,2:5,6-dibenzanthracene (I) (space group $P2_1/a$; 2 molecules per unit cell) is centrosymmetric, which eliminates a folded structure. From a chemical point of view the only structure compatible with a molecular centre of symmetry is planar or " essentially planar," and this has been confirmed by Iball and Young [7] using projections down the three principal crystallographic axes. There is thus a well-established experimental difference between the conformations of 9,10-dihydroanthracene and 9,10-dihydro-1,2:5,6-dibenzanthracene.



(I)

The present problem is to calculate the conformation of cyclohexa-1,4-diene, and to use similar theoretical considerations to explain the difference between the conformations of the other two compounds.

Calculation of Molecular Strain Energies

Fischer–Hirschfelder models show that there are two balancing factors: the cyclohexa-1,4-diene ring is strainless only in the folded conformation, and flattening it introduces angle strain; however, flattening the ring changes the distances between non-bonded hydrogen atoms and in particular increases the short distances between the hydrogen atoms marked * in formula (I) and the *lin* * hydrogen atoms of the methylene groups. Thus there are qualitative indications that the stable conformations of the cyclohexadiene and dihydroanthracene will be folded, while that of the dihydrodibenzanthracene be approximately planar. Detailed calculations substantiate these.

The interaction energy between non-bonded hydrogen atoms was calculated as follows. The distances between non-bonded hydrogen atoms were calculated for dihedral angles of the central cyclohexa-1,4-diene ring of 140°, 150° · · · 180°, bond lengths being assumed to be C–C 1·54, C=C 1·34, C–C (aromatic) 1·40, C–H 1·08 Å. All bond angles were assumed to be 120° in the flat conformation, except that the angles between the hydrogen atoms of the methylene groups were taken as 109° 28′. Symmetrical folding of the molecules about the axis through the methylene groups changed only the C–C–C angles at these groups. The approximation of maintaining the HCH angle constant for C–C–C angles varying between 109° 28′ and 120° is justified by quantum-mechanical calculations.[8] In the present work only those distances that changed with dihedral angle were calculated, as only energy differences between conformations were required; also only nearest neighbours were considered.

Three alternative functions have been suggested for interaction between non-bonded hydrogen atoms. The first is the function, labelled $V(^3\Sigma)$ in Fig. 1, which was calculated by Hirschfelder

* Nomenclature of ref. 1.

[2] Miyagawa, Morino, and Riemschneider, *Bull. Chem. Soc. Japan*, 1954, **27**, 177.
[3] Gerding and Haak, *Rec. Trav. chim.*, 1949, **68**, 293.
[4] Ferrier and Iball, *Chem. and Ind.*, 1954, 1296.
[5] Campbell, Le Fèvre, Le Fèvre, and Turner, *J.*, 1938, 404.
[6] Iball, *J.*, 1938, 1074.
[7] Iball and Young, *Acta Cryst.*, 1958, **11**, 476.
[8] Coulson and Moffitt, *Phil. Mag.*, 1949, **40**, 1.

and Linnett [9] for interaction between two hydrogen atoms in the triplet state (*i.e.*, with parallel electron spins); its use has been advocated by Howlett.[10] An alternative function, labelled $E_{H,H}$ in Fig. 1, is based on the approximation of perfect pairing and the assumption that the electron spins in the approaching hydrogen atoms have a random relative orientation; this function was first proposed by Eyring [11] (for a simplified discussion see Coulson [12]) and has been used recently by Adrian.[13] A third alternative which is rather similar to $E_{H,H}$ has been used by Pritchard and Sumner,[14] namely, $nV(^3\Sigma)$ where $n = 0{\cdot}5$. The present calculations are by the first two functions. Although the absolute magnitudes of the strain energies obtained differ considerably for the two [they are always larger for $V(^3\Sigma)$], the energy differences between the various conformations are similar. As a random relative orientation of electron spins appears more probable than a parallel orientation, the $E_{H,H}$ function appears the more suited to the present calculations.

The calculation of steric interaction energies is further complicated by the allowance for the variation of the van der Waals function with angle between the covalent-bond vector and the

FIG. 1. *Interaction energies between non-bonded hydrogen atoms.* $V(^3\Sigma)$ *is from the quantum-mechanical calculations* [9] *of the interaction between two hydrogen atoms in the triplet state.* $E_{H,H}$ *is from Eyring's formula.*[11]

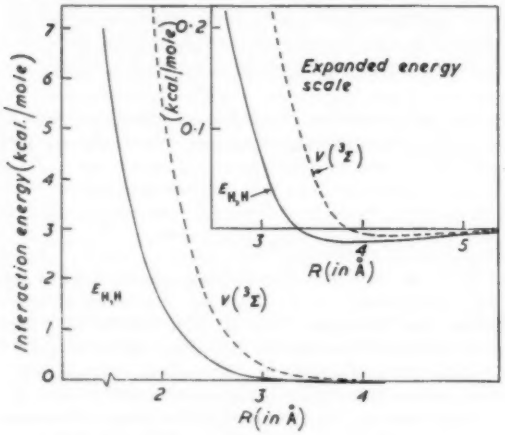
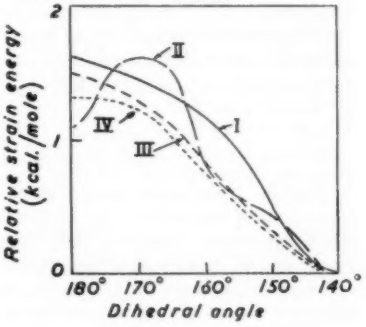


FIG. 2. *Curves of relative strain energy in cyclohexa-1,4-diene as a function of dihedral angle. Curves* (i) *and* (ii) *were calculated by using* $V(^3\Sigma)$, *without and with allowance for variation of van der Waals interaction with angle*; (iii) *and* (iv) *are analogous curves calculated with* $E_{H,H}$.



vector between the centres of the non-bonded atoms. For this Howlett's method was used.[10] These calculations have been carried out only for cyclohexa-1,4-diene, as the effects expected for the other two compounds are very small. Even for cyclohexa-1,4-diene the angular factor has little influence on the interaction energies (see Fig. 2).

Angle strain is absent from the ring only when the angles at the methylene-carbon atoms are 109° 28′; this occurs for a dihedral angle of about 141°. For other values of the dihedral angle, the strain in the ring will be least when the angle distortions are shared over the whole ring rather than concentrated at the methylene groups. On the simplifying assumption that the bending force constant is the same for all the angles of the ring, the angle-strain energy will be least when all the angle distortions are equal. In these circumstances the angle-strain energy will be close to one-third of what it would be had the angle strains been concentrated at the methylene groups. Sharing of the angle strain over the ring has been found experimentally in the dihydrodibenzanthracene, where the planar central ring has angles of 123° 24′, 115° 40′ (at the methylene group), and 122° 28′. With these assumptions and when the bending force constant for tetrahedral C–C–C bond angles is taken as the average value ($k_\delta = 0{\cdot}8 \times 10^{-11}$

[9] Hirschfelder and Linnett, *J. Chem. Phys.*, 1950, **18**, 130.
[10] Howlett, *J.*, 1958, 4353.
[11] Eyring, *J. Amer. Chem. Soc.*, 1932, **54**, 3191.
[12] Coulson, "Valence," Oxford Univ. Press, 1952, p. 166.
[13] Adrian, *J. Chem. Phys.*, 1958, **28**, 608.
[14] Pritchard and Sumner, *J.*, 1955, 1041.

erg/radian [2]), the angle-strain energy is given [15] by $E(\Delta\theta) = 6 \times 17{\cdot}5(\Delta\theta)^2$ cal./mole, where $\Delta\theta$ is the change in degrees from the nominal value of the angle (120° or 109° 28′). The changes in the bond angles produce small changes in the interatomic distances and hence in the steric-interaction energies, but no correction has been made for this.

FIG. 3. *Relative strain energy as a function of dihedral angle for* 9,10-*dihydroanthracene.*

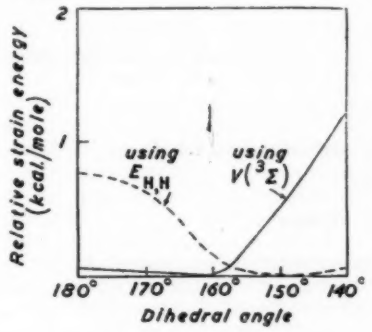
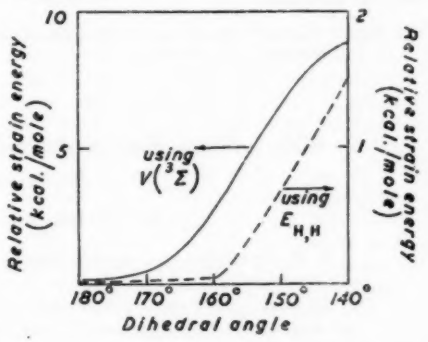


FIG. 4. *Relative strain energy as function of dihedral angle for* 9,10-*dihydro*-1,2:5,6-*dibenzanthracene.*



The total strain energy is given by the algebraic sum of steric-interaction energy and angle-strain energy, and the potential barrier between two conformations is obtained by taking the minimum value of the strain energy as zero. The results of the calculations are summarised in Figs. 2, 3, and 4, where the potential barriers are plotted as a function of dihedral angle for our three substances.

Discussion

The results for cyclohexa-1,4-diene show that the stable conformation has a dihedral angle of about 140°. The potential barrier to transformation from the " folded " to the " reverse folded " conformation is about 1·5 kcal./mole. The differences among the energy curves calculated for the various interaction functions considered are not large.

For 9,10-dihydroanthracene use of the $E_{H,H}$ function indicates a dihedral angle of about 150°, with a potential barrier of about 0·8 kcal./mole between the " folded " and the " reverse folded " conformations. The results for the $^3\Sigma$ interaction function are not as satisfactory; although there is a minimum at about 162°, it is very shallow, while the experimental dihedral angle of 145° gives a positive strain energy of 0·9 kcal./mole.

Both strain-energy curves obtained for the dihydrodibenzanthracene (I) indicate the planar conformation as the more stable; however, for this molecule the differences between the two curves are rather marked.

The stable conformations predicted by the calculations are in good agreement with experiment for 9,10-dihydroanthracene and 9,10-dihydro-1,2:5,6-dibenzanthracene, while that calculated for cyclohexa-1,4-diene favours the folded conformation. However, the calculated dihedral angle (about 140°) is not in very good agreement with that deduced from the dipole-moment measurements (about 160°).

For the two simpler molecules the potential barrier between the two stable conformations is small and thus there is no possibility of isolating a particular conformation of substituted derivatives. If anything, the heights of the potential barriers have been somewhat over-estimated by the present calculations, for the possibility of outward bending of C–H bonds has been neglected.

The method used in these calculations has two major defects. First, the molecules have been taken as rigid, whereas some relief of repulsion between non-bonded atoms will

[15] Westheimer in " Steric Effects in Organic Chemistry," ed. Newman, John Wiley and Sons, New York, 1956, p. 533.

be obtained by bending of C–C–H bond angles. Secondly, it has been assumed that the molecular vibrations will not change with conformation. Although both these simplifications will affect the heights and detailed shapes of the potential barriers, their effects do not appear to be large enough to alter the qualitative conclusions drawn from the calculations.

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NATIONAL PHYSICAL RESEARCH LABORATORY, C.S.I.R.,
PRETORIA, S. AFRICA. [*Received, December 18th*, 1958.]

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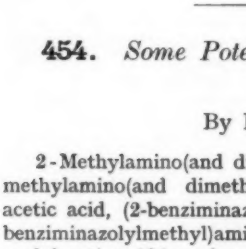
454. *Some Potential Chelating Agents derived from Benziminazole.*

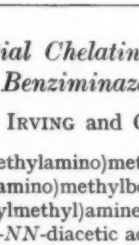
By H. IRVING and O. WEBER.

2-Methylamino(and dimethylamino)methylbenziminazole, 1-methyl-2-methylamino(and dimethylamino)methylbenziminazole, 1-benziminazolylacetic acid, (2-benziminazolylmethyl)amine-*NN*-diacetic acid, (1-methyl-2-benziminazolylmethyl)amine-*NN*-diacetic acid, and 2-2′-pyridyl-1-benziminazolylacetic acid have been prepared as potential chelating agents.

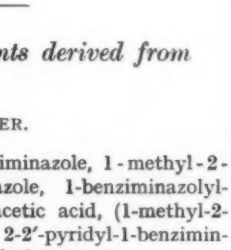
SINCE 2-aminomethylbenziminazole (I; R = R′ = R″ = H) forms a series of stable metal complexes,[1] several new derivatives of benziminazole, some of which contain the grouping $:N{\cdot}CH_2{\cdot}CH_2{\cdot}NH_{2-n}(CH_2{\cdot}CO_2H)_n$ ($n = 1$ or 2) characteristic of "complexones," have been prepared for examination as complexing agents.



(I)



(II)



(III)

2-Aminomethyl-1-methylbenziminazole (I; R = Me, R′ = R″ = H) was prepared from *N*-methyl-*o*-phenylenediamine (modified preparation) and ethyl aminoacetate hydrochloride following Lane's method for the preparation of 2-aminomethylbenziminazole itself.[2]

2-Dimethylaminomethylbenziminazole (I; R = H, R′ = R″ = Me) was best prepared from 2-chloromethylbenziminazole[3] and dimethylamine. 1-Methyl-2-methylaminomethylbenziminazole (I; R = R′ = Me, R″ = H) and 2-dimethylaminomethyl-1-methylbenziminazole (I; R = R′ = R″ = Me) were similarly prepared from 2-chloromethyl-1-methylbenziminazole and methylamine or dimethylamine, respectively.

1-Benziminazolylacetic acid (II) was readily obtained from benziminazole and chloroacetic acid under alkaline conditions, but attempts to extend this reaction to the preparation of 2-2′-pyridyl-1-benziminazolylacetic acid (III) were unsuccessful. However, this compound was prepared by hydrolysing the ester obtained by condensing 2-2′-pyridylbenziminazole[4] with methyl bromoacetate in the presence of anhydrous potassium carbonate.

(2-Benziminazolylmethyl)amine-*NN*-diacetic acid (I; R = H, R′ = R″ = $CH_2{\cdot}CO_2H$) was obtained by the hydrolysis of its dimethyl ester which resulted from the condensation

[1] Irving and Weber, *J.*, 1958, in the press.
[2] Lane, *J.*, 1957, 3313.
[3] Bloom and Day, *J. Org. Chem.*, 1939, **4**, 14.
[4] Leko and Vlajinac, *Bull. Soc. Chim. roy. Yougoslavie*, 1930, **1**, 3.

of 2-chloromethylbenziminazole[3] with dimethyliminodiacetate. The 1-methyl-derivative and its dimethyl ester were prepared similarly. (1-Methyl-2-benziminazolylmethyl)amine-*NN*-diacetic acid was also obtainable directly from 2-aminomethylbenziminazole and chloroacetic acid, but it has not proved possible to introduce a third $CH_2 \cdot CO_2H$ group in position 1 of the heterocyclic ring.

Experimental

N-*Methyl-o-phenylenediamine*.—The following procedure is based upon kinetic studies of the interaction of methyl iodide and *o*-phenylenediamine reported by Brown and Le Roi Nelson.[5] *o*-Phenylenediamine (35 g., 0·32 mole), methyl iodide (10·6 g., 0·16 mole), and methanol (400 ml.) were heated under reflux for 2 hr., then allowed to cool; more methyl iodide (10·6 ml., 0·16 mole) was added, and heating under reflux continued for a further 12 hr. Most of the methanol was distilled off, and the residue poured on crushed ice (1000 g.), basified with potassium hydroxide, and extracted with ether. The extracts were dried (K_2CO_3), the solvent removed under reduced pressure, and the residue fractionated in a vacuum. *N*-Methyl-*o*-phenylenediamine was obtained as a pale lemon-coloured oil, b. p. 116—120°/8 mm. (32 g., 82%), which, soon darkened.

2-*Aminomethyl*-1-*methylbenziminazole* (I; R = Me, R′ = R″ = H).—A mixture of finely ground ethyl aminoacetate hydrochloride (38·4 g., 0·25 mole) and freshly distilled *N*-methyl-*o*-phenylenediamine (32 g., 0·25 mole) was heated in a stream of nitrogen at 180—200° (oil-bath) for 3 hr. After being cooled, the residue was taken up in dilute hydrochloric acid, boiled with metal-free sugar-charcoal, and filtered. The filtrate was taken almost to dryness, and the residue triturated with ethanol, pale blue crystals separating. After repeated recrystallisation from hot ethanol 2-*aminomethyl*-1-*methylbenziminazole dihydrochloride* was obtained as colourless crystals, m. p. 257—259° (31 g., 50%) (Found: C, 46·4; H, 5·8; N, 17·9; Cl, 30·3. $C_9H_{11}N_3,2HCl$ requires C, 46·2; H, 5·6; N, 17·95; Cl, 30·3%).

1-*Methyl*-2-*methylaminomethylbenziminazole* (I; R = R′ = Me, R″ = H).—2-Chloromethyl-1-methylbenziminazole (7·5 g., 0·045 mole) [6] was added in small quantities to a solution of 9·8 ml. of 33% methylamine (2·8 g., 0·09 mole) in ether (50 ml.), the temperature being kept below 15°. After the initial reaction had subsided the mixture was kept at 35° for 3 hr. and then stored overnight at room temperature. Ether (150 ml.) was then added, the mixture cooled below 0°, and the precipitated methylamine hydrochloride collected. The filtrate was then saturated with dry hydrogen chloride. 1-*Methyl*-2-*methylaminomethylbenziminazole dihydrochloride* was collected, washed with ether, and recrystallised from ethanol, from which it separated as colourless needles, m. p. 186—187° (3·2 g., 29%) (Found: C, 48·4; H, 6·0; N, 17·1; Cl, 28·6. $C_{10}H_{13}N_3,2HCl$ requires C, 48·4; H, 6·1; N, 16·9; Cl, 28·6%).

2-*Dimethylaminomethyl*-1-*methylbenziminazole* (I; R = R′ = R″ = Me).—This was prepared similarly. The *dihydrochloride* crystallised from ethanol as long white needles, m. p. 244° (3·5 g., 32%) (Found: C, 50·1; H, 6·6; N, 15·8; Cl, 27·1. $C_{11}H_{15}N_3,2HCl$ requires C, 50·4; H, 6·5; N, 16·0; Cl, 27·05%).

1-*Benziminazolylacetic Acid* (II).—Chloroacetic acid (13·5 g., 0·125 mole) was dissolved in water (25 ml.) and neutralised with sodium hydroxide (5 g., 0·125 mole) in water (80 ml.). Benziminazole (9 g., 0·075 mole) was added, and the stirred solution heated to 80—90°. An almost saturated solution of sodium hydroxide (5 g., 0·125 mole) was added dropwise at such a rate that the pH of the solution was maintained for as long as possible between the change points of phenolphthalein and thymolphthalein. Towards the end of the reaction the mixture was allowed to become more alkaline, and when all the sodium hydroxide had been added heating was continued for 0·5 hr. at 80—90°. After being cooled, the solution was acidified with concentrated hydrochloric acid to pH 2—3, and the solid which separated was collected, washed with water and recrystallised thrice from boiling water. 1-*Benziminazolylacetic acid* formed crystals, m. p. 285—290° (7·5 g., 57%) (Found: C, 61·6; H, 4·6; N, 16·0. $C_9H_8O_2N_2$ requires C, 61·4; H, 4·6; N, 15·9%).

2-2′-*Pyridyl*-1-*benziminazolylacetic Acid* (III).—A finely ground mixture of 2-2′-pyridylbenziminazole (9·7 g., 0·05 mole) [4] and anhydrous potassium carbonate (13·8 g., 0·1 mole) was heated with methyl bromoacetate (15·3 g., 0·1 mole) under reflux for 8 hr. and then at a higher

[5] Brown and Nelson, *J. Amer. Chem. Soc.*, 1953, **73**, 24.
[6] Hughes and Lions, *Proc. Roy. Soc. N.S. Wales*, 1938, **71**, 209.

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temperature until reaction, as indicated by the evolution of carbon dioxide, had ceased (4 hr.). The brown resin was taken up in methanol (5 × 50 ml.) and separated from inorganic salts. The solvent was removed on the water-bath, and the residue fractionated *in vacuo*. Methyl 2-2′-pyridyl-1-benziminazolylacetate (7·5 g.), which distilled as a pale yellow oil at 80—100°/1 mm., was hydrolysed by hot aqueous 0·3N-barium hydroxide (150 ml.) for 1 hr. on the water-bath. The exactly equivalent amount of 2N-sulphuric acid was then added, and barium sulphate removed by centrifugation of the hot mixture. The centrifugate was evaporated to dryness, and the residue taken up in aqueous ethanol. *2-2′-Pyridyl-1-benziminazolylacetic acid* recrystallised from aqueous ethanol as white needles, m. p. 240° (subl.) (1 g., 8%) (Found: C, 66·1; H, 4·5; N, 16·7. $C_{14}H_{11}O_2N_3$ requires C, 66·4; H, 4·4; N, 16·6%).

(*2-Benziminazolylmethyl*)*amine-NN-diacetic Acid* (I; R = H, R′ = R″ = $CH_2{\cdot}CO_2H$).—(a) *From 2-aminomethylbenziminazole and chloroacetic acid.* 2-Aminomethylbenziminazole dihydrochloride (7·1 g., 0·03 mole) [2] in water (30 ml.) was neutralised with potassium hydroxide (3·37 g., 0·06 mole) in water (30 ml.). A solution of chloroacetic acid (9·9 g., 0·105 mole) in water (100 ml.), neutralised with potassium hydroxide (5·9 g., 0·105 mole), was added, and the mixture heated at 80—90° and shaken continuously while an almost saturated solution of potassium hydroxide (5·9 g., 0·105 mole) was added dropwise under the same conditions as in the preparation of (II), and the mixture was finally heated to boiling for 1·5 hr. After being cooled the solution was acidified to pH 3 with concentrated hydrochloric acid. The *diacetic acid* which separated was collected, well washed with water, and recrystallised thrice from boiling water, from which it separated as colourless crystals (4·5 g., 55%), m. p. 212° [Found: C, 55·0; H, 5·1; N, 16·0%; *M* (by titration), 261·7. $C_{12}H_{13}O_4N_3$ requires C, 54·8; H, 5·0; N, 16·0%; *M*, 263·2. Calc. for $C_{14}H_{15}O_6N_3$ (2-benziminazolylmethylamine-1 : *N* : *N*-triacetic acid): C, 52·3; H, 4·7; N, 13·1%; *M*, 321·3].

(b) *From 2-chloromethylbenziminazole and iminodiacetic ester.* An immediate reaction took place when the benziminazole (2·5 g., 0·015 mole) [3] was added to a solution of the ester (5 g., 0·03 mole) [7] in ethanol (10 ml.), accompanied by the separation of the hydrochloride of iminodiacetic ester. After being kept at room temperature for 0·5 hr. the mixture was heated on a water-bath (2 hr.) to complete the reaction, then filtered; dimethyl iminodiacetate hydrochloride remaining in the filtrate was removed by adding ether, cooling to below 0°, and filtration. The solvent was then evaporated, and the residue fractionally distilled *in vacuo*. Dimethyl (2-benziminazolylmethyl)amine-*NN*-diacetate (b. p. 110—120°/*ca.* 1 mm.) was hydrolysed as described above and gave the free acid (2 g., 45%), m. p. 212—214° after recrystallisation from hot water, identical with the previous specimen [Found: N, 15·9%; *M* (by titration), 262·5].

(*1-Methyl-2-benziminazolylmethyl*)*amine-NN-diacetic Acid* (I; R = Me, R′ = R″ = $CH_2{\cdot}CO_2H$).—2-Chloromethyl-1-methylbenziminazole (3·25 g., 0·018 mole) [6] was treated with a solution of dimethyl iminodiacetate (5·8 g., 0·036 mole) [7] in ethanol (10 ml.), and the product worked up as described in the previous preparation. (*1-Methyl-2-benziminazolylmethyl*)*amine-NN-diacetic acid* formed very pale yellow crystals, m. p. 186—188°, from hot water (2·2 g., 55%) (Found: C, 56·3; H, 5·6; N, 15·0. $C_{13}H_{15}O_4N_3$ requires C, 56·3; H, 5·45; N, 15·15%).

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[7] Dubsky, *Ber.*, 1917, **50**, 1694.

455. *Aromatic Reactivity. Part III.* Cleavage of Substituted Phenyltrimethylsilanes by Sulphuric Acid in Acetic Acid–Water.*

By F. B. Deans and C. Eaborn.

Use of a sulphuric acid–acetic acid–water medium for rate studies on the cleavage of phenyltrimethylsilanes has permitted measurement of the effects of strongly deactivating substituents. The results provide a detailed picture of the effects of a wide range of substituents on this electrophilic aromatic substitution.

The effects of some nuclear substituents, X, on the cleavage of a series of aryltrimethylsilanes, $X{\cdot}C_6H_4{\cdot}SiMe_3$, have been studied in aqueous-methanolic perchloric acid.[1] Use of sulphuric acid in acetic acid–water, in which greater variation in acidity is possible, permits a wider range of substituents to be studied, and, in particular, allows the effects of strongly electron-withdrawing groups to be measured. The medium consisted of a mixture of four volumes of acetic acid containing 0·73 wt.-% of water with three volumes of aqueous sulphuric acid; reference to a medium involving, say, 10·1M-sulphuric acid implies that the aqueous sulphuric acid taken was of this normality, not the final mixture.

Table 1. *Cleavage of* $X{\cdot}C_6H_4{\cdot}SiMe_3$ *in* H_2SO_4–$CH_3{\cdot}CO_2H$–H_2O *at* 50·18°.

$[H_2SO_4]$ [a] (M)	X	10^5k_1 (min.$^{-1}$)	$k_{rel.}$	$[H_2SO_4]$ (M)	X	10^5k_1 (min.$^{-1}$)	$k_{rel.}$
18·4	*p*-NO_2	1·56	$1{\cdot}22 \times 10^{-4}$	10·1	*p*-F	15·6	0·95
18·4	*p*-NMe_3^+	4·92	$3{\cdot}84 \times 10^{-4}$	10·1	H	16·3	1·00
18·4	*p*-CO_2H	18·9	—	10·1	*p*-Ph	46·1 [b]	2·83
16·4	*p*-CO_2H	4·72	$1{\cdot}48 \times 10^{-3}$	8·75	*p*-Ph	14·1	—
16·4	*m*-Cl	38·3	—	8·75	*o*-Ph	29·1	5·85
12·7	*m*-Cl	1·74	$1{\cdot}20 \times 10^{-3}$	6·41	*p*-Ph	1·82	—
12·7	*p*-Br	15·1	—	6·41	*p*-Me	11·6	18·0
10·1	*p*-Br	1·70	$1{\cdot}04 \times 10^{-1}$	5·65	*p*-Me	6·56	—
10·1	*p*-I	1·65	$1{\cdot}01 \times 10^{-1}$	5·65	(3-C_4H_3S) [c]	41·9	115
10·1	*p*-Cl	3·09	$1{\cdot}90 \times 10^{-1}$	1·15	(3-C_4H_3S) [c]	7·86	—
10·1	*m*-Ph	5·56	$3{\cdot}3 \times 10^{-1}$	1·15	*p*-$Me_3Si{\cdot}CH_2$	1·38	202
10·1	*m*-MeO	6·39	$3{\cdot}8 \times 10^{-1}$	1·15	*p*-MeO	6·93	1010

[a] See text and Experimental section. [b] Calc. from $k_{rel.}$ of 2·83 observed at 40·06°. [c] 3-Thienyltrimethylsilane; these figures are introduced for purposes of overlap and will be discussed later.

The reactions were followed spectrophotometrically. Table 1 lists the first-order rate constants, k_1, observed at 50·18°, and the rate, $k_{rel.}$, of cleavage of each compound relative to that of the unsubstituted compound, $C_6H_5{\cdot}SiMe_3$. These relative rates are obtained by stepwise change in the acidity, some compounds being examined in more than one medium to provide overlap. This procedure largely compensates for the change in the nature of the solvent, but the derived values of $k_{rel.}$ are not necessarily exactly those which would be obtained if all the compounds could be compared directly at one acid concentration.

Effects of some of the substituents in Table 1 have already been discussed;[1] the following are additional: *o*-Ph, *m*-Ph, *m*-MeO, *p*-I, *m*-Cl, *p*-CO_2H, *p*-NMe_3^+, and *p*-NO_2. The outstanding feature is the large deactivation brought about by the *p*-NO_2 group, which is a strong $-I$, $-T$ substituent.[2] The *p*-NMe_3^+ group, in spite of its positive charge which might be expected to repel very strongly the positively-charged attacking species, does not deactivate as strongly as the *p*-NO_2 group. The *para*-halogens deactivate in the order *p*-I = *p*-Br > *p*-Cl > *p*-F, the resultant influence of the *p*-F substituent being very small because its $+T$ effect almost balances out its $-I$ effect. The $+T$ effects of

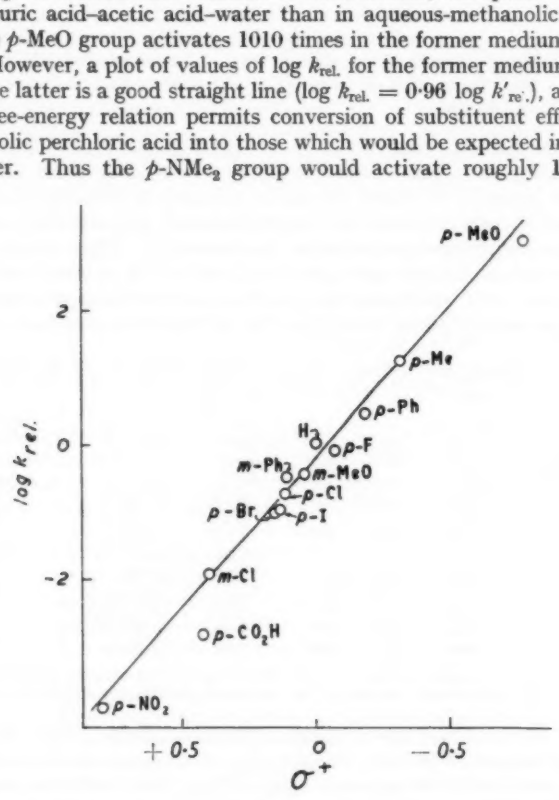
* Part II, *J.*, 1957, 4449.

[1] Eaborn, *J.*, 1956, 4858.

[2] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons, Ltd., London, 1953, Chap. VI.

the halogens cannot operate directly to the *meta*-position, and the *m*-Cl compound is about 16 times less reactive than the *p*-Cl compound. For similar reasons the MeO group, which activates strongly from *ortho*- and *para*-positions, deactivates some 2·6 times from the *meta*-position. The effects of phenyl substituents will be discussed in a later paper.

Over the range of substituents common to both studies, the spread of rates is rather smaller in sulphuric acid–acetic acid–water than in aqueous-methanolic perchloric acid; for example, the *p*-MeO group activates 1010 times in the former medium and 1510 times in the latter. However, a plot of values of log $k_{rel.}$ for the former medium [1] against those of log $k'_{rel.}$ for the latter is a good straight line (log $k_{rel.}$ = 0·96 log $k'_{rel.}$), and the existence of this linear free-energy relation permits conversion of substituent effects observed in aqueous methanolic perchloric acid into those which would be expected in sulphuric acid–acetic acid–water. Thus the *p*-NMe_2 group would activate roughly 10^7 times in the



latter medium and the *p*-OH substituent some 6000 times. The activating influence of the *p*-NMe_2 group, whose $+E$ effect may respond to the electron demand during the reaction, is thus much greater than the deactivating influence of the *p*-NO_2 group, whose $-E$ effect cannot come into play.[2]

In the Figure is a plot of the values of log $k_{rel.}$ against the substituent constants, σ^+, recently proposed for electrophilic aromatic substitutions or electrophilic side-chain reactions and derived from the rates of solvolysis of $\alpha\alpha$-dimethylbenzyl chlorides in 90% aqueous acetone.[3] With the exception of that for the *p*-CO_2H substituent, the points lie satisfactorily about a straight line, and the success of this use of the σ^+-constants is impressive in view of the range of substituents covered.* It is noteworthy that if the σ^+-constant for the *p*-CO_2Me group (0·49) is used for the *p*-CO_2H group in the Figure in place of the listed value (0·42), a point satisfactorily near the line is obtained, which suggests the possibility that, in spite of some contrary evidence,[4] slight ionization of the compound

* However, in future Parts attention will be drawn to some defects of the treatment.

[3] Brown and Okamoto, *J. Amer. Chem. Soc.*, 1958, **80**, 4979.

[4] Okamoto, Inukai, and Brown, *ibid.*, p. 4969.

p-$HO_2C{\cdot}C_6H_4{\cdot}CMe_2Cl$ occurs in the aqueous acetone used for measuring σ^+-constants. An alternative explanation, that the compound *p*-$Me_3Si{\cdot}C_6H_4{\cdot}CO_2H$ is considerably protonated in the cleavage medium, is less likely at the concentration of acid involved.

Activation Energies and Entropies.—In Table 2 are shown the apparent activation energies, E_a, and log A factors for the compounds studied. [log A = log k_1 + (E_a/2·303RT), with time in minutes.] Reactions were carried out at two temperatures only (50·18° and 40·06°), and the activation energies are probably not accurate in absolute terms to much better than ±1 kcal./mole. Within these limits there is no significant variation in E_a, whereas the effects of the substituents should reveal themselves in the activation-energy term. The reason for this apparent anomaly lies in the considerable change in medium necessary to give convenient rates with all the compounds. For example, the value of E_a for the *p*-Br compound in a medium involving 12·7M-sulphuric acid is 1·6 kcal./mole lower than that in a medium involving 10·1M-acid, and the difference is probably real, since relative activation energies determined on the same compound in two media are believed to be considerably more accurate than the relative activation energies determined for two compounds in the same medium. If the change from 10·1M- to 12·7M-acid causes the same lowering of the activation energy for all the compounds, then the activation energy for, say, the *m*-Cl compound in the former medium would be (22 + 1·6), *i.e.*, 23·6 kcal./mole. By this type of procedure it is possible to convert all the E_a values into approximate values of E_a (corr.), the activation energies which would be observed with 10·1M-acid. The rough values of E_a (corr.) show clearly a general fall from the unreactive *p*-NO_2 compound to the reactive *p*-MeO compound, as expected.

TABLE 2. *Activation energies and* $\log_{10}$ *A factors for cleavage of* X·C_6H_4·$SiMe_3$ *in* H_2SO_4–$CH_3{\cdot}CO_2H$–H_2O.

[H_2SO_4] (M)	X	E_a (kcal./mole)	$\log_{10} A$	E_A (corr.) (kcal./mole)	[H_2SO_4] (M)	X	E_a (kcal./mole)	$\log_{10} A$	E_A (corr.) (kcal./mole)
18·4	*p*-NO_2	20·9	12·30	24·8	10·1	*p*-F	20·8	13·34	20·8
18·4	*p*-NMe_3^+	19·3	11·77	23·2	10·1	H	20·7	13·22	20·7
18·4	*p*-CO_2H	20·5	13·15	—	10·1	*p*-Ph	20·0	13·06	20·0
16·4	*p*-CO_2H	20·8	12·72	24·4	8·75	*p*-Ph	21·2	13·50	—
16·4	*m*-Cl	20·0	13·11	—	8·75	*o*-Ph	20·5	13·30	19·3
12·7	*m*-Cl	22·0	13·10	23·6	6·41	*o*-Ph	21·8	13·37	—
12·7	*p*-I	19·3	12·22	20·9	6·41	*p*-Me	20·8	13·13	18·3
12·7	*p*-Br	19·5	12·32	—	5·65	*p*-Me	21·4	13·31	—
10·1	*p*-Br	21·1	12·49	21·1	5·65	(3-C_4H_3S) [a]	19·0	12·48	—
10·1	*p*-Cl	21·1	12·76	21·1	1·15	(3-C_4H_3S) [a]	22·2	12·91	—
10·1	*m*-Ph	21·8	13·45	21·8	1·15	*p*-$Me_3Si{\cdot}CH_3$	21·6	12·74	15·3
10·1	*m*-MeO	22·2	13·82	22·2	1·15	*p*-MeO	20·7	12·50	14·4

[a] See Table 1, footnote [e].

In principle similar corrections could be applied to log A, but Table 2 shows that there is no significant difference between the values determined for any compound in two different media, no doubt because of a fortuitous cancellation of influences. Except for the rather low value for the *p*-NMe_3^+ compound, log A is thus independent of the substituent present, at least within experimental error.* If it is assumed that a log A factor of 13·0 applies to all the compounds (except the *p*-NMe_3^+ derivative) in 10·1M-acid, then the values of $k_{rel.}$ in Table 1 would be accounted for by a fall in the activation energy from 27 for the *p*-NO_2 compound to 16·0 kcal./mole for the *p*-MeO compound.

The above discussion can profitably be brought to bear on a recent surprising conclusion that in de-deuteration of alkylbenzenes by trifluoroacetic acid–sulphuric acid the effects

* A low value of log A would be expected for the *p*-NMe_3^+ compound in reaction with a positively-charged species.[5] One can predict that the deactivating influence of the *p*-NMe_3^+ group relative to that of the *p*-NO_2 group would be markedly smaller in a reaction involving a neutral electrophil.

[5] Frost and Pearson, "Kinetics and Mechanism," John Wiley and Sons Inc., New York, 1953, p. 133.

of the alkyl substituents act solely through the entropy term, and not through the activation energy.[6] This conclusion was unjustified, and we believe it to be incorrect. It was reached because absence of effects due to the medium was inferred from the fact that the activation energies found for reaction of [$^2H_1$]-*p*-xylene in trifluoroacetic acid containing 0·1M- and 0·015M-sulphuric acid, respectively, differed by only 1 kcal./mole, *i.e.*, by little more than the estimated standard deviation of ±0·6 kcal./mole. It is more likely that this difference was real, and that considerable effects by the medium on the activation energy were involved over the range of sulphuric acid concentrations (0·015—2M). We suggest that such influences of the medium cancel out the effects of substituents, as in the reaction we have studied.

Experimental

Materials.—Acetic acid, purified by boiling it with chromium trioxide and subsequent fractionation, had m. p. 15·4° (corresponding with a water content of 0·73 wt.-%).

Diphenylyltrimethylsilanes were prepared from the appropriate chlorodiphenyls and trimethylchlorosilane by Wurtz–Fittig condensation in toluene, and had the following properties: 4-isomer, m. p. 55°; 3-isomer, b. p. 158°/10 mm., n_D^{20} 1·5686; 2-isomer, m. p. 38·5—39·0° (from EtOH) (Found: C, 79·6; H, 8·0%. Calc. for $C_{15}H_{18}Si$: C, 79·6; H, 8·0%). The m. p. of the 2-isomer was previously [7] given as 21·7°.

The methiodide of *p*-*NN*-dimethylaminophenyltrimethylsilane was prepared from the base and methyl iodide in methanol, the mixture being kept at 30° for 50 hr. The salt which separated on cooling was recrystallised to constant m. p. (200°, decomp.) from methanol. It was converted into the hydroxide by boiling its aqueous solution with silver oxide, filtering, and drying in a desiccator. The semi-crystalline mass was taken up in methanol, and the solution was filtered through a fine paper to remove particles of silver and silver salts. The methanol was evaporated off, and the residue was dried in a vacuum desiccator (P_2O_5), recrystallized from anhydrous ethanol by addition of dry ether, and stored over phosphoric oxide.

Other X·C_6H_4·$SiMe_3$ compounds used had the following properties: (X =)*p*-NO_2, m. p. 37°; *p*-CO_2H, m. p. 143°; *m*-Cl, b. p. 206—208°, n_D^{20} 1·5103; *p*-F, b. p. 173°, n_D^{20} 1·4742; H, b. p. 171·6°, n_D^{20} 1·4904; *m*-MeO, b. p. 213°, n_D^{20} 1·5025; *p*-Me, b. p. 191·5°, n_D^{20} 1·4930; *p*-Cl, b. p. 211·5°, n_D^{20} 1·5098; *p*-Br, b. p. 229·5°, n_D^{20} 1·5279. The last-named compound probably contained a little of the compounds *p*-Br·C_6H_4·Br and *p*-Me_3Si·C_6H_4·$SiMe_3$, neither of which interferes seriously with the rate studies.[1]

Rate Studies.—The general method is described in ref. 1. To 10 ml. of an acetic acid solution of the aryltrimethylsilane (of concn. shown in Table 3) were added 7·5 ml. of sulphuric acid, ice-cooling being used with 16M- and 18M-acid. Both volumes were delivered from fast-running burettes, the same burettes being used throughout. The mixture was shaken well and a sample was transferred to a 1 cm. stoppered cell in an Adkins's thermostatted cell holder (±0·03°) in a Unicam S.P. 500 spectrophotometer. Readings of the optical density, relative to a water blank at the wavelengths, λ, shown in Table 3, were begun after 8—10 min. and

Table 3.

X	Concn. (mM)	λ (mμ)	X	Concn. (mM)	λ (mμ)
p-NO_2	8	360	*m*-MeO	7	290
p-NMe_2^+	7	269	*p*-F	8	272
p-CO_2H	0·5	295, 293	H	10	269
m-Cl	8	279	*p*-Ph	3	294, 296
p-I	7	288, 289	*o*-Ph	7	290, 291
p-Br	8	274	*p*-Me	1·2	271
p-Cl	8	274	*p*-Me_3Si-CH_2	1	278, 279
m-Ph	4	290, 290·5	*p*-MeO	1·2	282

continued for at least 80% of reaction. Faster reactions were completed in the cell, but for slower runs " infinity " values of the optical density were obtained from samples of the reaction mixture kept in sealed tubes in a thermostat bath. Good first-order kinetics were observed; all rates were reproducible to ±1·5%, and usually to ±0·5%.

[6] Mackor, Smit, and van der Waals, *Trans. Faraday Soc.*, 1957, **53**, 1309.
[7] Clark, Gordon, Young, and Hunter, *J. Amer. Chem. Soc.*, 1951, **73**, 3798.

The possibility of interference by sulphonation or sulphondesilylation (*i.e.*, the reaction $X{\cdot}C_6H_4{\cdot}SiMe_3 + H_2SO_4 \longrightarrow X{\cdot}C_6H_4{\cdot}SO_3H + HO{\cdot}SiMe_3$) was ruled out as follows: (i) The spectrum of a solution of benzene in the medium used for cleaving phenyltrimethylsilane (involving 10·1M-sulphuric acid) did not change during 5 hr. at 50°. A slight change occurred with 18·1M-acid, but so slowly as to make it clear that no significant sulphonation would occur in the case of strongly deactivated rings (*i.e.*, with p-CO_2H, p-NMe_3^+ and p-NO_2 substituents). The spectrum of naphthalene (which is readily sulphonated) did not change in the medium involving 6·41M-acid. (ii) The spectra of the solutions obtained by cleaving the p-CO_2H and p-Ph compounds in media involving 18·4 and 8·75M-sulphuric acid, respectively, were identical (within 3%) with those of solutions of benzoic acid and diphenyl of corresponding concentrations in the same media. This indicates that significant sulphondesilylation does not occur.

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NOTES.

456. *Aromatic Reactivity. Part IV.* The 2- and the 3-Position of Thiophen in Protodesilylation.*

By F. B. DEANS and C. EABORN.

THE 2-position of thiophen is known to be very reactive towards electrophilic substitution, but no quantitative data on the reactivity are available. The 3-position is considerably less reactive, and it is known that detritiation by aqueous sulphuric acid takes place 955 ± 140 times as readily at the 2-position.[1] Molecular-orbital calculations suggest that the 3-position should be about as reactive as a single position of benzene and the 2-position considerably more reactive.[2]

It has been established that the rate of acid cleavage of the aryl–silicon bond in a substituted phenyltrimethylsilane (protodesilylation) provides an excellent measure of reactivity at the aromatic carbon of the bond,[3,4] and we have now used the cleavage to measure the reactivity of the 2- and the 3-position of thiophen. We find that in acetic acid containing aqueous sulphuric acid at 50·18°, 2-thienyltrimethylsilane is cleaved 43·5 times as fast as the 3-isomer, which in turn is cleaved 6·4 times as fast as p-tolyltrimethylsilane. Since the last compound is cleaved 18 times as fast as phenyltrimethylsilane,[3] the 2- and the 3-thienyl compounds are 5000 and 115 times as reactive as the phenyl compound. We conclude with confidence that, while the 3-position of thiophen is considerably less reactive than the 2-position, it is nevertheless markedly more reactive than a single position of benzene. It is of interest that the reactivity of the 3-thienyl compound is about half that of p-hydroxyphenyltrimethylsilane.[3]

The results here presented are consistent with the relative reactivites observed for thiophen in detritiation if a linear free-energy relation is assumed between substituent effects in detritiation and in desilylation. The p-methyl group activates about 240 times in detritiation by aqueous sulphuric acid,[5] and about 18 times in desilylation by aqueous sulphuric acid in acetic acid,[3] and the ratio of the logarithms (to base 10) of these values is 1·90. 2-Thienyltrimethylsilane is 43·5 times as reactive as the 3-isomer, and thus the logarithm of the ratio of the reactivites of the 2- and the 3-position of thiophen in detritiation should be 1·90 × log 43·5, *i.e.*, 3·1. In view of the extrapolations involved this represents good agreement with the experimental figure [1] of 2·98 ± 0·06.

* Part III, preceding paper.

[1] Halvarson and Melander, *Arkiv Kemi*, 1955, **8**, 29.
[2] Melander, *ibid.*, 1955, **8**, 361; Heer, *J. Amer. Chem. Soc.*, 1954, **76**, 4802.
[3] Deans and Eaborn, *J.*, 1959, 2299.
[4] Eaborn, *J.*, 1953, 3148, and 1956, 4858; Benkeser and Krysiak, *J. Amer. Chem. Soc.*, 1954, **76**, 6353; Benkeser, Hickner, and Hoke, *ibid.*, 1958, **80**, 2279; Benkeser, Hickner, Hoke, and Thomas, *ibid.*, p. 5289.
[5] Eaborn and Taylor, unpublished work.

Experimental.—Thienyltrimethylsilanes. 2-Thienyltrimethylsilane, b. p. 165·5°, n_D^{20} 1·4996, was prepared from 2-thienyl-lithium and trimethylchlorosilane in ether.

A little ethyl bromide was added to magnesium turnings (22 g.) and ether (150 ml.). When reaction had started a mixture of 3-bromothiophen (24 g.), ethyl bromide (82 g.), and ether (450 ml.) was added slowly with stirring, and addition was followed by 40 hours' refluxing.[6] Trimethylchlorosilane (100 g.) was added at such a rate as to maintain boiling, and the mixture was then boiled for 3 hr. Water and then dilute acid were added until two clear layers separated. The ether layer was washed and dried (Na_2SO_4), and fractionation gave *3-thienyltrimethylsilane* (12 g.), b. p. 168°, n_D^{20} 1·4993 (Found: C, 53·7; H, 7·6. $C_7H_{12}SSi$ requires C, 53·8; H, 7·8%).

Rate studies. The method has been described.[3]

Wavelengths of 252 and 253 mμ were used for the 3-isomer and 255 mμ for the 2-isomer. Good first-order kinetics were observed.

The Table shows the first-order rate constants, k_1, at 50·18° and the activation energies (accurate to ±1 kcal./mole), E_a, and $\log_{10} A$ factors determined from measurements at two temperatures only.

Compound	H_2SO_4 * (M)	k_1 (min.$^{-1}$)	E_a (kcal./mole)	$\log_{10} A$
p-Me·C_6H_4·$SiMe_3$	5·65	0·0656	21·4	13·3
3-C_4H_3·$SiMe_3$	5·65	0·419	19·0	12·5
3-C_4H_3·$SiMe_3$	1·15	0·00786	22·2	12·9
2-C_4H_3·$SiMe_3$	1·15	0·342	19·5	12·7

* Concn. of acid, 3 vol. of which were added to 4 vol. of a solution of the organosilane in acetic acid containing 0·73 wt.-% of water (see ref. 3).

THE UNIVERSITY, LEICESTER. [*Received, February* 13*th*, 1959.]

[6] Gronowitz, *Arkiv Kemi*, 1954, **7**, 267.

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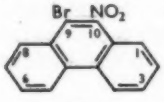
457. *The Nitration of 9-Bromophenanthrene.*

By R. S. W. BRAITHWAITE and P. F. HOLT.

THE only bromomononitrophenanthrene described in the literature, 9-bromo-10-nitrophenanthrene (I), was prepared by nitrating 9-bromophenanthrene in benzene with dinitrogen tetroxide [1,2] or in hot acetic acid with nitric acid.[3-6] The yields are low and 3-nitro-9 : 10-phenanthraquinone is also formed.[4,5] Whilst attempting to improve the method, we investigated the mechanism by which the phenanthraquinone is formed.



(I)

Although insoluble, 9-bromophenanthrene slowly turns yellow in cold nitric acid (*d* 1·42). After some hours, treatment of the solid with acetone yields a residue from which a second bromomononitrophenanthrene, m. p. 192°, and a small quantity of the 9-bromo-10-nitro-compound can be separated. On evaporation, the mother-liquor gives a mixture from which both these two and a third bromomononitrophenanthrene, m. p. 153°, have been isolated, the last in small yield.

Oxidation of the second bromonitrophenanthrene with chromium trioxide yields 3-nitro-9 : 10-phenanthraquinone, proving that the nitro-group is in either the 3- or the 6-position. Reduction with zinc and hydrochloric acid gives 3-amino-9-bromophenanthrene, the orientation of which has been established.[7] Therefore, the compound is 9-bromo-3-nitrophenanthrene.

Hot fuming nitric acid in acetic acid oxidized it to 3-nitro-9 : 10-phenanthraquinone.

[1] Schmidt and Kämpf, *Ber.*, 1902, **35**, 3121.
[2] Schmidt and Ladner, *Ber.*, 1904, **37**, 3573.
[3] Anschütz, *Ber.*, 1878, **11**, 1217.
[4] Werner, *Annalen*, 1902, **321**, 334.
[5] Austin, *J.*, 1908, **93**, 1760.
[6] Callow and Gulland, *J.*, 1929, 2424.
[7] Schultz, Goldberg, Ordas, and Carsch, *J. Org. Chem.*, 1946, **11**, 307.

The formation of this phenanthraquinone during the nitration of 9-bromophenanthrene in hot solution probably therefore involves the production and subsequent oxidation of 9-bromo-3-nitrophenanthrene, the 10-nitro-group preventing the oxidation of the 9 : 10-bridge in the isomer (I).

Chromium trioxide oxidises the third bromomononitrophenanthrene to a mononitrophenanthraquinone not identical with the known 2-, 3-, or 4-nitrophenanthraquinone, and which is therefore 1-nitrophenanthraquinone; the bromonitrophenanthrene must be either the 9-bromo-1-nitro- or the 9-bromo-8-nitro-compound.

Experimental.—Nitration of 9-*bromophenanthrene.* Finely powdered 9-bromophenanthrene (20 g.) was added during 30 min. to nitric acid (*d* 1·42; 200 ml.) at 18°. After 10 hr. the solid was filtered off, washed with water, boiled with acetone (100 ml.), cooled, filtered off, and again boiled with acetone (100 ml.) and cooled. The residue (10 g.) was crystallised from acetic acid. The first crop formed yellow needles of 9-*bromo*-3-*nitrophenanthrene* (7·4 g.), m. p. 189—191°, raised on recrystallisation to 192° (Found: C, 55·7; H, 2·7; N, 4·7; Br, 26·0. $C_{14}H_8O_2NBr$ requires C, 55·7; H, 2·7; N, 4·6; Br, 26·5%). The second crop, on recrystallisation, gave pale yellow needles of 9-bromo-10-nitrophenanthrene (I) (1·3 g.), m. p. 202—205°, which did not depress the m. p. of an authentic specimen.

The acetone mother-liquors, on concentration at room temperature, deposited a solid (2·6 g.). Fractional crystallization from acetic acid gave the 9-bromo-10-nitro-compound (I) (0·35 g.), and 9-*bromo*-(1 *or* 8)-*nitrophenanthrene* (III) (44 mg.), yellow needles, m. p. 153°; mixed with (I), m. p. 135—140°; mixed with (II), m. p. 132—150° (Found: C, 55·6; H, 3·0; N, 5·0. $C_{14}H_8O_2NBr$ requires C, 55·7; H, 2·7; N, 4·6%).

Oxidation of 9-*bromo*-3-*nitrophenanthrene.* Chromium trioxide (0·2 g.) was added in portions to 9-bromo-3-nitrophenanthrene (0·1 g.) in acetic acid (30 ml.) at 90°. After 2 hr. the mixture was poured into water, and the precipitate was separated and recrystallized from acetic acid, giving 3-nitro-9 : 10-phenanthraquinone (39 mg.), m. p. 279—280° (lit.,[1] m. p. 279—280°); oxime, m. p. 237—238° (lit.,[1] m. p. 240°).

Reduction of 9-*bromo*-3-*nitrophenanthrene.* To 9-bromo-3-nitrophenanthrene (0·3 g.) in boiling ethanol (80 ml.) were added hydrochloric acid (*d* 1·18; 10 ml.) and then zinc dust (0·2 g.). After refluxing, the filtered solution when concentrated gave 3-*amino*-9-*bromophenanthrene hydrochloride* (0·35 g.), white needles, m. p. 258° (decomp.) (Found: C, 54·2; H, 4·2. $C_{14}H_{11}NBrCl$ requires C, 54·4; H, 3·6%), converted by ethanolic sodium hydroxide into 3-amino-9-bromophenanthrene, white needles (from aqueous ethanol), m. p. 113° (lit.,[7] m. p. 112·5—113°) (Found: C, 60·9; H, 3·6; N, 5·0; Br, 30·0. Calc. for $C_{14}H_{10}NBr$: C, 61·8; H, 3·7; N, 5·2; Br, 29·4%) (Schultz *et al.*[7] gave N, 5·37%); acetyl derivative, m. p. 221° (lit.,[7] m. p. 220·5—221·5°).

Oxidation of 9-*bromo*-3-*nitrophenanthrene with nitric acid.* Nitric acid (*d* 1·5; 3 ml.) was added dropwise to 9-bromo-3-nitrophenanthrene (2 g.) in acetic acid (9 ml.) and acetic anhydride (4·5 ml.) at 90°. After 20 min., the liquid on cooling yielded a precipitate which, when recrystallized from toluene, was identified as 3-nitro-9 : 10-phenanthraquinone (0·16 g.), m. p. 271—278°, mixed m. p. 278—279°.

Oxidation of 9-*bromo*-(1 *or* 8)-*nitrophenanthrene.* Chromium trioxide (25 mg.) in acetic acid (10 ml.) was added in portions to the bromonitrophenanthrene (19 mg.) in acetic acid (10 ml.) at 90°. After 2·5 hr. the mixture was diluted with water (30 ml.) and filtered. The orange precipitate, recrystallized from aqueous acetic acid, gave 1-*nitrophenanthraquinone* (5 mg.) as orange prisms, decomposing slowly above about 240° to give a purple sublimate, and finally melting at 270° (Found: C, 64·5; H, 2·72. $C_{14}H_7O_4N$ requires C, 66·2; H, 2·77%). This material depressed the m. p.s of authentic 2-nitrophenanthraquinone and authentic 3-nitrophenanthraquinone. 4-Nitrophenanthraquinone has m. p. 180°.[8] The new phenanthraquinone dissolves in sulphuric acid to give a greenish-brown solution.

The authors are indebted to the Department of Scientific and Industrial Research for a Maintenance Allowance to one of them (R. S. W. B.), to Miss M. L. Booker for technical assistance, and to one of the Referees for helpful advice.

College of Science and Technology, Manchester.
University of Reading. [*Received, September 5th*, 1958.]

[8] Schmidt and Kämpf, *Ber.*, **1903**, **36**, 3734.

458. *An Aporphine Alkaloid, Nuciferine, from Asiatic Lotus Cultivated in Hong Kong.*

By H. R. Arthur and H. T. Cheung.

Asiatic lotus (*Nelumbo nucifera* Gaertn.) is an endemic species which occurs widely in the Colony of Hong Kong. It is found also in regions from India to Australia, is eaten, and is used in folk-medicine. Leaves, of Hong Kong origin, afforded us a 0·02% yield of an alkaloid, whose hydrochloride was more soluble in chloroform than in cold dilute hydrochloric acid or water, thus providing a simple method of isolation. Analysis and determination of the molecular weight indicated that the alkaloid, which we have named nuciferine, has the formula $C_{16}H_{12}(OMe)_2(\supset NMe)$; it has a blue fluorescence in the solid state or in solution and, after irradiation with ultraviolet light, a yellow phosphorescence. The physical constants of nuciferine and of its derivatives corresponded with those of (—)-5 : 6-dimethoxyaporphine (dimethylnor-roemerine),[1] and identity was confirmed by a mixed melting point and comparison of the infrared spectrum with that of a sample prepared from roemerine by Cooke and Haynes.[2]

An alkaloid, nelumbine (no m. p. or formula given), from the seed and cotyledons of lotus,[3] may or may not be the same as nuciferine.

Amino-acids and other alkaloids have been reported to occur in other (Japanese) species of the Nymphaeaceae.[4] Several Nymphaeaceae alkaloids of unknown constitution are recorded by Henry.[5]

Experimental.—Analyses are by Dr. Zimmermann, Melbourne. Fresh leaves (6 kg.) of *Nelumbo nucifera*, collected in September, were extracted with cold ethanol (14 l.) for 4 days. The solvent was removed from the green extract under reduced pressure. The black residue was distributed between chloroform (3 l.) and 5% aqueous ammonia (1 l.). The chloroform layer was washed with water and shaken several times with 2N-hydrochloric acid. [From the acid extract (4 l.) a brown basic oil was obtained; this did not yield nuciferine.] The residue obtained on removal of the chloroform under reduced pressure was triturated with warm water (2 l.). The aqueous solution was basified with ammonia and then extracted with chloroform (2 l.), from which, on distillation, the crude base (1·2 g.) was obtained. Recrystallisation from ethanol gave *nuciferine*, m. p. 165·5° (Kofler), $[\alpha]_D^{22}$ −157·5° (*c* 1·06 in ethanol) (Found: C, 77·7; H, 7·1; N, 4·7; OMe, 20·8; NMe, 4·6%; *M*, 279. $C_{19}H_{21}O_2N$ requires C, 77·3; H, 7·2; N, 4·7; 2OMe, 21·0; NMe, 5·1%; *M*, 295).

Dry hydrogen chloride was passed into a solution of nuciferine (0·5 g.) in dry ether. The white gel formed was collected. Crystallisation from ether–methanol gave needles of *nuciferine hydrochloride*, m. p. 241° (vac.) (Found: C, 68·8; H, 6·6. $C_{19}H_{21}O_2N,HCl$ requires C, 68·8; H, 6·7%). Nuciferine (0·25 g.) was warmed with methyl iodide (20 ml.) for a few minutes; removal of the methyl iodide left *nuciferine methiodide* which crystallised from ethanol as needles, m. p. 177—178° (Kofler) (Found: C, 54·3; H, 5·7; N, 2·6. $C_{19}H_{21}O_2N,MeI$ requires C, 54·9; H, 5·5; N, 3·2%) (Yunusov *et al.*[1] give m. p. 164—167°).

The colour reactions of nuciferine were as those published for synthetic (±)-5 : 6-dimethoxyaporphine,[6] except that with Fröhde's reagent the blue colour became brown.

The authors thank Mr. R. G. Cooke (University of Melbourne) for the sample of (—)-5 : 6-dimethoxyaporphine, and for determination of infrared spectra; Mr. H. C. Tang (Government Herbarium, Hong Kong) for identification of plant material; Smith, Kline & French Laboratories, Philadelphia, and the Research Grants Committee of the University of Hong Kong, for grants-in-aid.

University of Hong Kong, Hong Kong. [*Received, November 24th*, 1958.]

[1] Yunusov, Konovalova, and Orekhov, *Bull. Soc. chim. France*, 1940, **7**, 70; *J. Gen. Chem., U.S.S.R.*, 1939, **9**, 1868.
[2] Cooke and Haynes, *Austral. J. Chem.*, 1954, **7**, 99.
[3] Greshoff and Boorsma, *Mededeel. s'Lands Plantent.*, 1899, **31**, 125.
[4] Ukai, Arata, Ohashi, and Seto, *Ann. Report Fac. Pharm., Kanazawa Univ.*, 1953, **3**, 8.
[5] Henry, "The Plant Alkaloids," J. & A. Churchill Ltd., London, 4th edn., 1949, p. 758.
[6] Gulland and Haworth, *J.*, 1928, 590; Callow, Gulland, and Haworth, *J.*, 1929, 670.

459. *The Alcoholysis of Aromatic Acid Chlorides.*

By E. R. A. Peeling.

Recent investigations of the kinetics of the hydrolysis and alcoholysis of benzoyl and substituted benzoyl chlorides have not led to completely concordant conclusions. Hudson and his co-workers [1,2] have suggested that aromatic acid chlorides may be hydrolysed by either the S_N1 or the S_N2 mechanism, and Bunton and Lewis [3] have suggested a two-stage process. We now present some results which we believe support the mechanisms proposed by Bunton and Lewis.

The rates of ethyl alcoholysis in initially neutral solution of the acyl halides studied are shown in Table 1, and the rates in the presence of added alkali in Table 2. The relative

Table 1. *First-order rate coefficients (k_1 in sec.$^{-1}$) of the alcoholysis of* X·C_6H_4·COCl *in "* 80% *" alcoholic acetone at* −10·75°.

X	H	*p*-NO_2	*p*-Me	2 : 4 : 6-Me_3
10^6k_1	4·97	212	2·25	521

Table 2. *Second-order rate coefficients (k_2 in sec.$^{-1}$ mole^{-1} l.) of reaction between* X·C_6H_4·COCl (0·03M) *and* OEt^- (0·02M) *in "* 80% *" alcoholic acetone at* −10·75°.

X	H	*p*-NO_2	2 : 4 : 6-Me_3
k_2	>3	>3	0·34

rates of alcoholysis of the four acyl halides are qualitatively similar to the relative rates in aqueous solvents. In the presence of alkali the rates are much increased (Table 2). The rate of the solvolytic reaction is so much less than that of the reaction with alkali that the solvolytic reaction may be neglected.

These results are similar to those of Bunton and Lewis,[3] who calculated an increase of nearly 1000-fold in the rate of hydrolysis of 2 : 4 : 6-trimethylbenzoyl chloride in 95% aqueous dioxan in the presence of 1M-alkali. Brown and Hudson,[2] on the other hand, found no increase in the rate of hydrolysis on the addition of 0·001M-alkali. It seems possible that in this case the potassium nitrate used to eliminate junction potentials in the titration cell prevents the alkali dissolving in the solvent to give a homogeneous solution.

An alternative explanation * is that the increase of rate of the neutral solvolysis and the reduction of the rate of nucleophilic attack by hydroxide ions caused by the addition of potassium nitrate result in no apparent alkaline catalysis.

The increase in rate of alcoholysis caused by the addition of alkali and the effect of added salts, shown in Table 3, rule out the possibility that even 2 : 4 : 6-trimethylbenzoyl chloride reacts by an S_N1-like mechanism and support the findings and conclusions of Bunton and Lewis.[3]

Table 3. *First-order rate coefficients* (10^4 k_1; k_1 *in sec.*$^{-1}$) *of the alcoholysis of* p-*nitro- and* 2 : 4 : 6-*trimethyl-benzoyl chloride in "* 80% *" alcoholic acetone at* −10·75° *in the presence of* 0·1M-LiCl *and* 0·1M-LiBr.

Halide	No salt added	0·1M-LiCl	0·1M-LiBr
p-NO_2·C_6H_4·COCl	2·12	3·42	5·96
2 : 4 : 6-$Me_3C_6H_2$·COCl	5·21	5·20	9·46

Experimental.—Materials. Acetone was purified by the method of Conant and Kirner.[4] Ethyl alcohol was dried by the method of Lund and Bjerrum.[5] Ethyl-alcoholic acetone ("80%")

* The author is grateful to a Referee for this suggestion.

[1] Hudson and Wardill, *J.*, 1950, 1729; *J.*, 1950, 1731; Archer and Hudson, *J.*, 1950, 3259; Brown and Hudson, *J.*, 1953, 883; Archer, Hudson, and Wardill, *J.*, 1953, 888.
[2] Brown and Hudson, *J.*, 1953, 3352.
[3] Bunton and Lewis, *Chem. and Ind.*, 1956, 180.
[4] Conant and Kirner, *J. Amer. Chem. Soc.*, 1924, **46**, 246.
[5] Lund and Bjerrum, *Ber.*, 1931, **64**, 210.

was prepared by mixing 8 vol. of acetone with 2 vol. of dry ethyl alcohol. Sufficient solvent was prepared to carry out all the kinetic measurements on the same batch.

Benzoyl chloride, distilled at atmospheric pressure and protected from moisture, had b. p. 198°. *p*-Nitrobenzoyl chloride, recrystallised from dry light petroleum (b. p. 60—80°), had m. p. 75°. *p*-Toluoyl chloride, prepared from *p*-toluic acid by thionyl chloride and purified by distillation at reduced pressure, had b. p. 118°/20 mm. 2 : 4 : 6-Trimethylbenzoyl chloride was prepared from mesitylene by bromination, conversion of the product into the acid *via* the Grignard reagent by means of carbon dioxide, and treatment of the acid with thionyl chloride. The chloride was purified by distillation under reduced pressure, and then had b. p. 120°/20 mm. Lithium chloride and bromide were heated at 180° for 3 hr. and cooled over P_2O_5.

Rate measurements. These were carried out by the sampling method. For each run ~0·03 mol. of acyl halide was added to solvent (70 ml.) at −10·75°. Samples (5 ml.) were run into acetone (70 ml.) cooled to ~−50° to stop the reaction and were titrated with ~0·03N-potassium hydroxide, lacmoid being used as indicator. For runs in the presence of alkali, the required amount of sodium was dissolved in cold solvent before addition of the acyl halide, and the reaction followed by titration with 0·01N-hydrochloric acid. The following is a typical run with 0·0218M-2 : 4 : 6-trimethylbenzoyl chloride: samples (5 ml.) were titrated with 0·0276N-potassium hydroxide:

Time (sec.)	0	217	372	623	918	1235	1552	2500	∞
Titre (ml.)	0·00	0·44	0·72	1·08	1·46	1·86	2·18	2·86	3·94
10^4k_1 (sec.$^{-1}$)	—	5·4	5·4	5·2	5·1	5·2	5·2	5·2	—

The formula $k_2 = 2{\cdot}303[\log_{10} b(a-x)/a(b-x)]/t(a-b)$ was used to calculate the second-order rate coefficient of the run on 2 : 4 : 6-trimethylbenzoyl chloride in the presence of alkali; a and b are the molarities of the alkali and acyl halide, respectively. The rates of the reactions of benzoyl and *p*-nitrobenzoyl chlorides in alkaline solution were too fast to be measured, and the rates given in Table 2 assume the half-life period of the reaction with alkali of average concentration 0·02M to be <10 sec.

The author thanks Professor E. D. Hughes, F.R.S., for much helpful advice.

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460. *A Molecular-orbital Calculation of the Ultraviolet Absorption Spectra of* 1 : 5- *and* 1 : 8-*Naphthyridine.*

By T. E. PEACOCK.

VARIOUS methods of calculating the electronic absorption spectra of heterocyclic molecules have been compared.[1,2] One of these, employing SCF (self-consistent field) molecular orbitals of the parent hydrocarbon, was found particularly satisfactory under certain well-defined conditions: in other cases it was necessary to incorporate self-consistency in the substituted system. The two types of SCF calculation are here applied to interpret the spectral shifts which accompany di-nitrogen substitution in naphthalene to give naphthyridines.

Spectra of 1 : 5- *and* 1 : 8-*Naphthyridine.*—Naphthalene (numbered as in I), which has the symmetry D_{2h}, is converted into naphthyridine by the substitution of two C–H groups by nitrogen atoms. The ultraviolet spectrum of naphthalene, calculated by use of SCF molecular orbitals, has already been discussed.[2] The energies of its two highest occupied and two lowest unoccupied SCF molecular orbitals are indicated in the Figure, along with symmetry symbols.

The 1 : 8-naphthyridine molecule has the reduced symmetry C_{2v}. The ground state function Φ_0 and the functions of the excited configurations $\Phi(A \longrightarrow A')$, $\Phi(B \longrightarrow B')$, $\Phi(A \longrightarrow B')$, $\Phi(B \longrightarrow A')$ are grouped according to symmetry under C_{2v} as follows,

[1] McWeeny, *Proc. Phys. Soc.*, 1957, *A*, **70**, 593.
[2] Peacock, *Proc. Phys. Soc.*, 1957, *A*, **70**, 654.

where $\Phi(A \longrightarrow A')$, for instance, is the singlet function in which the configuration is $(A)^1(A')^1$ instead of $(A)^2$:

A.....	Φ_0	$\Phi(A \longrightarrow B')$	$\Phi(B \longrightarrow A')$
B.....	—	$\Phi(A \longrightarrow A')$	$\Phi(B \longrightarrow B')$

Since there are excited functions of the same symmetry as the ground state function, mixing will be allowed and should be adequate to describe the perturbing effecting of the substituents without the necessity for revising the basic orbitals.[1]

Energies and symmetries of the naphthalene SCF molecular orbitals. β is the resonance integral for the C–C *bond in benzene.*

B' ———— $-1{\cdot}12\beta$ (B_3)
A' ———— $-0{\cdot}92\beta$ (B_3)

A ———— $0{\cdot}92\beta$ (B_1)
B ———— $1{\cdot}12\beta$ (A)

(I)

The symmetry of the 1 : 5-naphthyridine molecule is C_{2h}. The ground state function Φ_0 and the excited state functions are grouped according to symmetry as follows:

A_u	Φ_0			
B_g	$\Phi(A \longrightarrow A')$	$\Phi(B \longrightarrow \overline{B'})$	$\Phi(A \longrightarrow \overline{B'})$	$\Phi(B \longrightarrow \overline{A'})$

Here the effects of the nitrogen atoms on the ground state cannot be described by the limited configuration interaction because this is symmetry-forbidden: to describe the perturbed molecule we must introduce orbitals appropriate to the substituted molecule, *i.e.*, SCF molecular orbitals for 1 : 5-naphthyridine. These can be obtained by an iterative method, starting from the solution for the hydrocarbon.[3]

The general interpretation of the so-called α, p, β, and β' bands of an alternant hydrocarbon [4,5] and its heterocyclic derivatives [2,6,7] in terms of the mixing of the configurational functions discussed above, is now well known. The electron-interaction integrals and parameters were given the same numerical values as in previous work.[2,6] Our calculated transition energies for the naphthyridines are given in the Table, with those for naphthalene.[2]

State and symmetry	Transition energy (predicted) ($\bar{\nu}$)	Observed band ($\bar{\nu}$)	State and symmetry	Transition energy (predicted) ($\bar{\nu}$)	Observed band ($\bar{\nu}$)	State and symmetry	Transition energy (predicted) ($\bar{\nu}$)	Observed band ($\bar{\nu}$)
Naphthalene			1 : 5-Naphthyridine *			1 : 8-Naphthyridine *		
$\alpha(B_3)$	35,900	32,300	$\alpha(B_g)$	36,300	32,450	$\alpha(B)$	36,150	32,450
$p(B_3)$	36,600	36,500	$p(B_g)$	37,100	37,450	$p(A)$	37,100	37,450
$\beta(B_3)$	51,000	45,200	$\beta(B_g)$	53,050	>47,600	$\beta(B)$	53,950	>45,200
$\beta'(B_3)$	53,700	59,700	$\beta'(B_g)$	53,050		$\beta'(A)$	54,150	

* The experimental values for these two molecules were personally communicated by Dr. S. F. Mason, University of Exeter.

All the theoretical values above are absolute and no attempt has been made to fit the observed data by revising parameter values or otherwise.

Discussion.—α Band. Theory predicts the band to move 400 $\bar{\nu}$ for 1 : 5-naphthyridine and 250 $\bar{\nu}$ for 1 : 8-naphthyridine: experimentally the band moves 150 $\bar{\nu}$. Although the agreement between the calculated and observed energies is only fair, on an absolute scale, it is most significant that the theoretical shifts are of the correct order of magnitude and in the right direction. It is predicted that substitution will increase the intensity of the band,[2,4] as observed.

[3] McWeeny, *Proc. Roy. Soc.*, 1956, *A*, **237**, 355.
[4] Dewar and Longuet-Higgins, *Proc. Phys. Soc.*, 1954, *A*, **67**, 795.
[5] Pople, *Proc. Phys. Soc.*, 1955, *A*, **68**, 81.
[6] McWeeny and Peacock, *Proc. Phys. Soc.*, 1957, *A*, **70**, 41.
[7] Peacock, *Nature*, 1957, **179**, 684.

p Band. On substitution this band moves to higher energies by 950 $\bar{\nu}$ in both cases. It is predicted to move 500 $\bar{\nu}$ this way in both systems. Because of the uncertainty in determining the centre of this band we may say that agreement between theory and experiment is again fair. An increase in the intensity of the band in both substituted systems is observed, again agreeing with theory.

β *and* β′ *Bands.* Experimentally the positions of these bands are uncertain. According to Mason they are certainly higher than 47,600 $\bar{\nu}$ in 1 : 5-naphthyridine and higher than 45,200 $\bar{\nu}$ in 1 : 8-naphthyridine. Our predictions of about 53,000 $\bar{\nu}$ in each case seems to support this. Both bands will be decreased in intensity [2,4] but as the bands are so close a single broad intense band should result in both substituted molecules. Mason has confirmed the presence of a single intense band in 1 : 8-naphthyridine.

I thank Dr. R. McWeeny for his interest, Dr. S. F. Mason for allowing me to quote unpublished results, and the Ramsay Memorial Fellowships Trust for a Fellowship.

UNIVERSITY COLLEGE OF NORTH STAFFORDSHIRE, KEELE. [*Received, December 8th,* 1958.]

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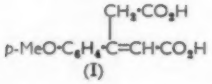
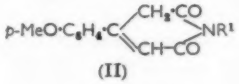
461. N-*Hydroxy-imides. Part III.*[1] β-p-*Methoxyphenylglutaconimides.*

By D. E. AMES and T. F. GREY.

(With spectroscopic data by MISS E. M. TANNER.)

THE preparation of the *N*-benzyloxy- and *N*-hydroxy-imides of some dibasic acids has been described.[1,2] We have now prepared some derivatives of β-*p*-methoxyphenylglutaconic acid (I), which is readily obtained by condensation of anisole with acetonedicarboxylic acid.[3] Condensation of the acid (I) with benzyloxyamine in boiling xylene yielded the *N*-benzyloxy-imide (II; $R^1 = O{\cdot}CH_2Ph$), tautomeric with the pyridone (III; $R^1 = O{\cdot}CH_2Ph$, $R^2 = H$). The latter was debenzylated to the *N*-hydroxy-imide or pyridone (II; $R^1 = OH$ or III; $R^1 = OH$, $R^2 = H$) which was methylated to 1 : 6-dimethoxy-4-*p*-methoxyphenylpyrid-2-one (III; $R^1 = OMe$, $R^2 = Me$).


(I)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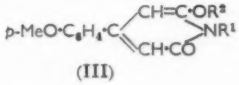
(III)

Methylation of the *N*-benzyloxy-imide (II; $R^1 = O{\cdot}CH_2Ph$) afforded 1-benzyloxy-6-methoxy-4-*p*-methoxyphenylpyrid-2-one (III; $R^1 = O{\cdot}CH_2Ph$, $R^2 = Me$) which, on catalytic debenzylation, gave 1-hydroxy-6-methoxy-4-*p*-methoxyphenylpyrid-2-one (III; $R^1 = OH$, $R^2 = Me$).

The isomeric 6-hydroxy-1-methoxy-4-*p*-methoxyphenylpyrid-2-one (III; $R^1 = OMe$, $R^2 = H$) was obtained from *O*-methylhydroxylamine and β-*p*-methoxyphenylglutaconic anhydride (attempts to use the glutaconic acid failed).

Spectroscopic Data (By MISS E. M. TANNER).—Structures (II) and (III) are readily differentiated spectroscopically (see Table). In infrared spectra of compounds (II) there are two carbonyl bands typical of the group ·CO·NR·CO·, while compounds (III) show amide carbonyl absorption near 1660 $cm.^{-1}$. Most of the pyridones (II) show weak hydroxyl bands in spectra of chloroform solutions which are not present in spectra in

[1] Part II, *J.*, 1955, 3518.
[2] Ames and Grey, *J.*, 1955, 631.
[3] Limaye and Bhave, *J. Indian Chem. Soc.*, 1931, **8**, 137.

Compound	pK_a' [a]	Infrared spectrum [c] OH	C=O	Ultraviolet spectrum 0·1N-HCl $\lambda_{max.}$	ε	0·1N-NaOH $\lambda_{max.}$	ε
(II; R^1 = OH)	4·63 [b]	3232 [d]	1726, 1675	223	13,200	258	9,600
				318	15,650	328	5,610
(II; R^1 = OMe)	3·89	3504 [e] w	1726, 1684	223	13,050	260	21,000
				319	17,750	336	9,300
(II; R^1 = O·CH_2Ph)	5·77 [b]	3536 [e] w	1729, 1691	235	7,240	248	21,100
				293	6,300	337	8,650
(II; R^1 = Me)	5·57	—	1712, 1661	220	15,600	260	23,300
				312	18,800	340	8,600
(II; R^1 = CH_2Ph)	decomp.	—	1703, 1660	—	—	263	24,730
						344	8,360
(II; R^1 = Ph)	5·43 [b]	3536 [e] w	1715, 1665	225 sh	14,300	263	24,400
				312	19,790	325	5,740
(III; R^1 = OH = R^2 = Me)	7·13	3378	1650	285	19,200	285	19,550
(III; R^1 = OMe, R^2 = Me)	>11		1661	222	15,930		
				228	19,500	288	19,500
(III; R^1 = O·CH_2Ph, R^2 = Me)	>11		1658	289	21,400	288	21,900

[a] In 50% ethanol. [b] In 66% ethanol. [c] cm.$^{-1}$; measured in chloroform. [d] Measured in Nujol. [e] No band in corresponding Nujol spectrum. w, weak band. sh, shoulder. Infrared spectra were recorded with a Grubb-Parsons DP1/S3A spectrometer and ultraviolet spectra with a Unicam S.P. 500 spectrophotometer.

Nujol; this indicates that the compounds are tautomeric in solution and is confirmed by their behaviour as acids of medium strength, pK_a' 4—6, and their ultraviolet spectra which differ in acid and alkaline solution. The pyridones (III) are not titratable as acids (except III; R^1 = OH, R^2 = H) and their ultraviolet spectra are unchanged by change of pH.

Experimental.—Preparation of imides from β-p-*methoxyphenylglutaconic acid.* (i). Ethanolic methylamine (50 c.c.; 33%) was added gradually to the glutaconic acid [3] (15 g.). The solution was then distilled slowly so that the bath temperature reached 200° after 1 hr. After the residue had been heated at 190—200° for a further 1 hr., the residual gum was triturated with ether. Recrystallisation from ethanol yielded needles of β-p-*methoxyphenyl*-N-*methylglutaconimide* (2·5 g.), m. p. 197—199° (Found: C, 67·9; H, 5·7; N, 5·9. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·7; N, 6·0%).

(ii). A mixture of the glutaconic acid (10 g.), benzylamine (5 g.), and xylene (100 c.c.) was refluxed through a Dean and Stark phase separator until no more water could be collected (2 hr.). After removal of xylene (30 c.c.) by distillation, the hot solution was filtered. N-*Benzyl*-β-p-*methoxyphenylglutaconimide*, which separated on cooling, formed pale yellow prisms (3·3 g.) (from ethanol), m. p. 150—152° (Found: C, 74·0; H, 5·8; N, 4·7. $C_{19}H_{17}O_3N$ requires C, 74·3; H, 5·6; N, 4·6%).

(iii). *O*-Benzylhydroxylamine (31 g.) and the glutaconic acid (56 g.) were condensed in xylene (900 c.c.) as in the previous example. The *imide* (4·3 g.) separated from 2-methoxyethanol as hexagonal plates, m. p. 214—125° (Found: C, 70·4; H, 5·4; N, 4·3. $C_{19}H_{17}O_4N$ requires C, 70·6; H, 5·3; N, 4·3%).

N-*Hydroxy*-β-p-*methoxyphenylglutaconimide*. The benzyloxy-compound (28 g.) was hydrogenated in ethanol (400 c.c.) over palladised charcoal (3 g.; 10%). Absorption ceased when 1 mole of hydrogen had been taken up and the mixture was then filtered at the b. p. On cooling the *imide* (11 g.) separated; recrystallisation from 2-methoxyethanol gave prisms, m. p. 216—217° (Found: C, 62·0; H, 5·2; N, 5·6. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·8; N, 6·0%).

1 : 6-*Dimethoxy*-4-p-*methoxyphenylpyrid*-2-*one*. Ethereal diazomethane (from 25 g. of methylnitrosourea) was added to a suspension of the dihydroxy-pyridone (1·4 g.) in methanol (200 c.c.), and the mixture was set aside overnight. After addition of acetic acid (1 c.c.), the solution was evaporated to dryness under reduced pressure. Recrystallisation of the residue from ethyl acetate–light petroleum (b. p. 60—80°) furnished the *pyridone* as prismatic needles, m. p. 129—130° (Found: C, 64·2; H, 5·8; N, 5·1; MeO, 35·7. $C_{14}H_{15}O_4N$ requires C, 64·4; H, 5·8; N, 5·4; MeO, 35·6%).

1-*Benzyloxy*-6-*methoxy*-4-p-*methoxyphenylpyrid*-2-*one*. The *N*-benzyloxy-imide (5 g.) was suspended in methanol (100 c.c.) and treated with ethereal diazomethane (from 20 g. of methylnitrosourea). After 20 min. all the solid had dissolved, and acetic acid was added to destroy

excess of diazomethane. Evaporation of the solvent, trituration of the residue, and crystallisation from ethyl acetate gave the *pyridone* (3·8 g.), m. p. 142—143° (Found: C, 70·7; H, 5·4; N, 4·2. $C_{20}H_{19}O_4N$ requires C, 71·2; H, 5·7; N, 4·2%).

1-*Hydroxy*-6-*methoxy*-4-p-*methoxyphenylpyrid*-2-*one*. A suspension of the benzyloxy-compound (10 g.) in ethanol (250 c.c.) was hydrogenated in the presence of 10% palladised charcoal (2 g.). Absorption ceased after about one mole of hydrogen had been taken up. The solution was filtered at the b. p., and on cooling the filtrate deposited the *pyridone* (6·3 g.), m. p. 194—196° (after crystallisation from ethanol) (Found: C, 62·8; H, 5·3; N, 5·8; OMe, 24·5. $C_{13}H_{13}O_4N$ requires C, 63·2; H, 5·3; N, 5·7; OMe, 25·1%). An alcoholic solution with ferric chloride had an intense red coloration.

O-Methylacetoxime. Acetoxime (108 g.) was added to a hot solution of sodium butoxide [from sodium (36 g.) in butanol (750 c.c.)], and methyl iodide (210 g.) was then added with occasional shaking at such a rate that the mixture refluxed gently. After being kept overnight the mixture was distilled. The fraction, b. p. 65—80°, was left over calcium chloride for 2 days and then refractionated to give the ether (b. p. 70—73°) (40 g.).

N-*Methoxy*-β-p-*methoxyphenylglutaconimide*. *O*-Methylhydroxylamine hydrochloride (7·5 g., obtained by hydrolysis of *O*-methylacetoxime [4]) was added to an ice-cold mixture of ether (100 c.c.) and potassium hydroxide solution (20 g. in 20 c.c. of water). The mixture was shaken vigorously for 5 min., and the organic layer decanted, the aqueous layer being washed with more ether (2 × 50 c.c.). The combined ethereal layers were dried (KOH) and added to a suspension of β-*p*-methoxyphenylglutaconic anhydride [3] (11 g.) in xylene (100 c.c.) and methanol (50 c.c.). After 30 min. the solution was distilled slowly (bath at 100° after 1 hr.). Xylene (200 c.c.) was added and distillation was resumed (a total of 250 c.c. of distillate was collected). On cooling crystals separated, and repeated recrystallisation from methanol gave the *imide* as needles, m. p. 163—166° (Found: C, 63·2; H, 5·4; N, 5·6; OMe, 24·9. $C_{13}H_{13}O_4N$ requires C, 63·2; H, 5·3; N, 5·7; OMe, 25·1%).

The authors are grateful to Dr. R. E. Bowman for discussion and to Mr. F. Oliver for microanalyses.

PARKE, DAVIS & COMPANY, HOUNSLOW, MIDDLESEX. [*Received, January 2nd*, 1959.]

[4] Dunstan and Goulding, *J.*, 1901, **79**, 630.

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462. *Ultraviolet Spectra and Periodate Oxidation of Monosaccharide Phenylhydrazones.*

By J. J. O'DONNELL and ELIZABETH PERCIVAL.

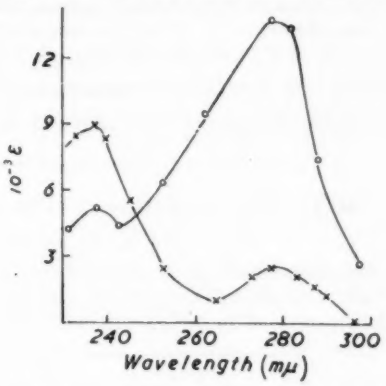
IN work on the repeated Barry degradation of laminarin and cladophoran [1] it became apparent that the periodate ion attacked the nitrogen-containing residues present in the degraded polysaccharides, the nitrogen content being reduced on subsequent oxidation. To obtain information on the nature of these nitrogen-containing residues and quantitative values for the amount of periodate reduced by these groups in the degraded polysaccharide the ultraviolet absorption spectra of, and the action of periodate on, sugar phenylhydrazones have been studied. It was expected that the uptake of periodate by such compounds might be related to that of the degraded polymers.

The ultraviolet spectra of sugar osazones [2] and of the Barry degradation fragments of monomethyl-sugars [3] have already been examined. The spectra of the sugar phenylhydrazones exhibited qualitative and quantitative similarities, but these could not be related to the spectra of the degraded polysaccharides. When the solutions were kept the phenylhydrazone spectra changed to a non-characteristic curve, in keeping with the tendency of these compounds to decompose in solution.

Oxidation of sugar osazones [4] by sodium periodate resulted in rapid consumption of

[1] O'Donnell and Percival, *J.*, 1959, 1739.
[2] Barry, McCormick, and Mitchell, *J.*, 1955, 222.
[3] Mitchell, *Proc. Roy. Irish Acad.*, 1958, **59**, 43.
[4] Chargaff and Magasanik, *J. Amer. Chem. Soc.*, 1947, **69**, 1459; Courtois, Wickstrom, and Le Dizet, *Bull. Soc. chim. France*, 1952, 1006.

the theoretical amount of periodate, and precipitation of mesoxaldehyde 1 : 2-bisphenylhydrazone; this was followed by a slow irregular reduction which was attributed to interaction of the periodate ion with the insoluble mesoxaldehyde derivative. A similar reaction takes place with the phenylhydrazones, and orange-red crystals believed to be glyoxal monophenylhydrazone are deposited. The initial rapid consumption of periodate was complete within an hour and corresponded to the number of glycol groups. This was followed by a further uptake of 1·6—2·8 mol. during 3 days. These results, together with the earlier results on periodate oxidation of osazones, demonstrate clearly that the periodate ion attacks, not only the glycol groups, but also the nitrogenous group in the degraded polymers. Since oxidation of degraded nitrogen-containing polysaccharides is usually allowed to proceed for several days the extent of this attack is considerable and any quantitative conclusions based on it must be viewed with caution.



Ultraviolet absorption of (○) *monosaccharide phenylhydrazones and* (×) *the Skraup form of glucose phenylhydrazone.*

In this work it was found that, whereas the β-form of glucose phenylhydrazone had adsorption characteristics similar to those of the other sugar phenylhydrazones, the Skraup isomer [4] of glucose phenylhydrazone gave a different spectrum (see Figure) which was qualitatively similar to that of phenylhydrazine. This agrees with the results of Mester and Major [5] who postulated, on the basis of the formation of a crystalline formazan, that glucose β-phenylhydrazone (like mannose phenylhydrazone) had an acyclic structure. In contrast, Skraup's glucose phenylhydrazone did not yield a formazan and was therefore considered to have a cyclic structure.

Experimental.—The phenylhydrazones of mannose, ribose, arabinose, galactose, and glucose (β-form and Skraup form), prepared by the standard method,[6] were isolated as white crystalline solids and recrystallised to constant m. p. The absorption of each phenylhydrazone (10 mg./l.) in 1 : 1 aqueous ethanol was measured in a Unicam S.P. 500 spectrophotometer in the range 222—230 mμ. The value of ε at 277 mμ for each sugar was constant (±10%) at 13,700. A second less well-defined peak at 235—240 mμ was also present. The Skraup isomer had a negligible absorption at 277 mμ but at 237 mμ had ε 8900 (cf. phenylhydrazine which also has a maximum absorption at this wavelength). Degraded laminarin and degraded cladophoran (142 mg./l.) showed weak absorption peaks at 383—385 and 360—362 mμ respectively.

Periodate oxidation. Samples (100 mg.) were dissolved in water (5 ml.) (mannose phenylhydrazone gave a suspension), and 0·197M-sodium periodate solution) (15 ml.) was added. The reaction was followed by withdrawal of samples at intervals, and the amount of periodate reduced was measured.[7] The quantity of periodate (3 or 4 mols.) required to cleave the glycol groups present in each hydrazone was consumed within 1 hr. and this was accompanied by the precipitation of orange-red crystals. As oxidation proceeded these crystals gradually redissolved

[5] Mester and Major, *J. Amer. Chem. Soc.*, 1955, **77**, 4297.
[6] Butler and Cretcher, *J. Amer. Chem. Soc.*, 1929, **51**, 3161; Fischer, *Ber.*, 1887, **20**, 824.
[7] Fleury and Lange, *Compt. rend.*, 1932, **195**, 1395.

and a tar resulted; this had no distinguishing feature in its ultraviolet spectrum. The periodate consumptions (mole/mole) were:

Period of oxidn.	galactose	Phenylhydrazones of: glucose β-isomer	glucose Skraup isomer	arabinose	ribose
30 min.	4·05	3·90	3·95	3·06	3·16
72 hr.	6·30	6·20	6·80	4·60	4·90

The orange-red crystals consumed 1 mole of periodate per mole (calculated as glyoxal monophenylhydrazone) during 30 min. and 2·6 moles per mole during 48 hr.

If the oxidation was stopped after 30 min. by addition of ethylene glycol and sodium hydrogen carbonate the crystalline material could be separated (80% yield calculated as glyoxal monophenylhydrazone). After one recrystallisation from alcohol this had m. p. 85° (decomp.) (Found: N, 18·4. Calc. for $C_9H_9ON_3$: N, 18·9%).

One of us (J. J. O'D.) thanks the Institute of Seaweed Research for a maintenance grant.

CHEMISTRY DEPARTMENT, UNIVERSITY OF EDINBURGH. [*Received, January 9th,* 1959.]

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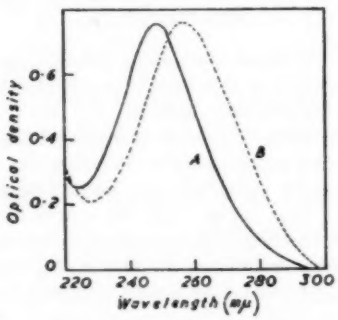
463. *The Ionization Constant of* p-*Iodobenzoic Acid at* 25°.

By R. A. ROBINSON and K. P. ANG.

THE ionization constants of many substituted benzoic acids have been determined, notably by Dippy and his colleagues,[1] but, although Kuhn and Wassermann [2] found pK 5·00 for *p*-iodobenzoic acid in 50% methanol at 20°, no measurements seem to have been made



Absorption spectra of $1·3 \times 10^{-5}$N-p-*iodobenzoic acid:* 4 *cm. cells.*
(*A*) *Alkaline solution.*
(*B*) *Acid solution.*

for aqueous solutions. This may be due to the low solubility of the acid in water and the method of ultraviolet spectrophotometry [3] therefore commends itself.

p-Iodobenzoic acid from Koch Laboratories was twice sublimed *in vacuo* at 100° (m. p. 271—272°) and optical density measurements were made with solutions $1·76 \times 10^{-5}$N with respect to the acid, 4 cm. cells being used in a Uvispek instrument. The temperature was maintained at 25° ± 0·5° in an air-conditioned room. The Figure shows the absorption spectra in solutions of pH 0 and pH 12. It will be seen that there is no wavelength at which the absorption is negligible in one solution and appreciable in the other; this diminishes the accuracy of the method but at a wavelength of 270 mμ there is sufficient difference between absorption in acid and in alkaline solution to make the method applicable. Two sets of buffers were used. The first consisted of formic acid partially neutralized with sodium hydroxide. If K_R is the ionization constant of formic acid, then:

$$pK_R = pH - \log \frac{Salt}{Acid} - \log \gamma_F \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

[1] Bray, Dippy, Hughes, and Laxton, *J.*, 1957, 2405.
[2] Kuhn and Wassermann, *Helv. Chim. Acta*, 1928, **11**, 31.
[3] Robinson and Biggs, *Trans. Faraday Soc.*, 1955, **51**, 901; Biggs, *J.*, 1956, 2485.

where $pH = -\log \gamma_H m_H$, γ_F is the activity coefficient of the formate ion, and the ratio salt : acid is corrected for the appreciable ionization of formic acid.

If K is the ionization constant of *p*-iodobenzoic acid, then:

$$pK = pH - \log \frac{D_1 - D}{D - D_2} - \log \gamma_B \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where D_1, D_2, and D are the optical densities in solutions of pH 0 and 12 and in the formate buffer respectively, and γ_B is the activity coefficient of the iodobenzoate ion. Then:

$$pK = pK_R + \log \frac{\text{Salt}}{\text{Acid}} - \log \frac{D_1 - D}{D - D_2} \quad . \quad . \quad . \quad . \quad . \quad (3)$$

if γ_F can be equated to γ_B. It is known [4] that $pK_R = 3{\cdot}754$ at 25°.

The second set consisted of partially neutralized succinic acid with the addition of sodium chloride, *i.e.*, either *x*M-succinic acid + 0·5*x*M-sodium hydrogen succinate + *x*M-sodium chloride or a buffer with half this amount of sodium chloride. In either case, sufficient data are available [5] to afford the log (salt/acid) term in equation (3).

The tabulated results were obtained.

p-Iodobenzoic acid, $1{\cdot}76 \times 10^{-5}$N. Wavelength, 270 mμ, 4 cm. cells. Temp., 25°.
D_1 (in M-HCl) 0·760. D_2 (in 0·01M-NaOH) 0·311.

Molality of $H{\cdot}CO_2H$	D	log (Salt/Acid)	log $(D_1 - D)/(D - D_2)$	pK
	Formic acid, *x*M.	Sodium formate, 1·923*x*M.		
0·001733	0·491	0·321	0·175	3·900
0·003466	0·497	0·304	0·150	3·908
0·006932	0·502	0·295	0·130	3·919
	Formic acid, *x*M.	Sodium formate, 1·504*x*M.		
0·001989	0·520	0·222	0·060	3·916
0·003978	0·525	0·201	0·041	3·914
0·007956	0·533	0·190	0·029	3·915
	Formic acid, *x*M.	Sodium formate, *x*M.		
0·002533	0·565	0·059	−0·115	3·928
0·005066	0·572	0·033	−0·142	3·929
0·01013	0·574	0·018	−0·150	3·922

Molality of succinic acid	D	log (Salt/Acid)	log $(D_1 - D)/(D - D_2)$	pK
Succinic acid, *x*M.	Sodium hydrogen succinate, 0·5*x*M.		Sodium chloride, *x*M.	
0·02	0·550	−0·315	−0·056	3·948
0·03	0·549	−0·321	−0·052	3·938
0·04	0·551	−0·326	−0·060	3·941
0·05	0·551	−0·328	−0·060	3·939
Succinic acid, *x*M.	Sodium hydrogen succinate, 0·5*x*M.		Sodium chloride, 0·5*x*M.	
0·02	0·545	−0·318	−0·037	3·926
0·03	0·549	−0·332	−0·052	3·937
0·04	0·550	−0·324	−0·056	3·939
0·05	0·551	−0·327	−0·059	3·939

The average value of pK is 3·927 with a standard deviation of 0·010. The succinate give higher pK's than the formate buffers, and a further study on an acid more suited to the method is needed to see if the difference is real. For the present, we report the best value of pK as 3·93. The Hammett σ parameter is therefore 0·27, compared with 0·276 derived by Hammett [6] from measurement on the alkaline hydrolysis of ethyl benzoates in 88% ethanol at 30°.

UNIVERSITY OF MALAYA, SINGAPORE. [*Received, January 19th*, 1959.]

[4] Harned and Embree, *J. Amer. Chem. Soc.*, 1934, **56**, 1042.
[5] Pinching and Bates, *J. Res. Nat. Bur. Stand.*, 1950, **45**, 444.
[6] Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 188.

464. N-*Alkyl*-2-1′-*benzimidazolylethylamines.*

By S. Bell, R. Foster, and (Miss) W. E. B. Soutar.

Certain *N*-alkyl-2-1′-benzimidazolylethylamines have been prepared in order to discover whether they resemble or antagonise serotonin in its pharmacological action.

2-1′-Benzimidazolyl-*N*-methylethylamine (II; R = H, R′ = Me) has been prepared from the corresponding unsubstituted compound (II; R = R′ = H) by formylation and subsequent reduction with lithium aluminium hydride, but the overall yield starting from

o-chloronitrobenzene is low. The same product has, however, been obtained in high yield by reducing the condensation product (I; R = H, R′ = Me) of benzimidazole and α-chloro-*N*-methylacetamide This method has been applied to the preparation of the *NN*-dimethyl and *NN*-diethyl derivatives. The latter compound has also been prepared from *NN*-diethyl-*N*′-*o*-nitrophenylethylenediamine (III; R = R′ = Et) by reduction and cyclisation.

Experimental.—2-1′-*Benzimidazolyl*-N-*methylethylamine.* (*a*) 2-1′-Benzimidazolylethylamine [1] (3·5 g.), 98—100% formic acid (10 ml.), and toluene (40 ml.) were slowly distilled on a steam-bath. After 6 hr. the residual formic acid and toluene were evaporated *in vacuo*, water (2 ml.) was added, the mixture basified with solid potassium hydrogen carbonate and extracted with chloroform. The dried (Na_2SO_4) solution gave, on evaporation, a brownish-oil which slowly solidified. 2-1′-*Benzimidazolyl*-*N*-*formylethylamine* was obtained after two recrystallisations from ethyl acetate as needles (15%), m. p. 148·5° (Found: C, 63·6; H, 5·9; N, 22·2. $C_{10}H_{11}ON_3$ requires C, 63·5; H, 5·8; N, 22·2%). The formyl compound (0·9 g.) was added slowly to a suspension of lithium aluminium hydride (1 g.) in tetrahydrofuran and then refluxed with stirring for 4 hr., the excess of hydride decomposed with water, and the product extracted with benzene. Evaporation gave an oil, soluble in water from which 2-1′-*benziminazolyl*-N-*methylethylamine dipicrate* was precipitated. Two crystallisations from water gave red needles (70%), decomp. *ca.* 170° (Found: C, 42·1; H, 3·2. $C_{10}H_{13}N_3,2C_6H_3O_7N_3$ requires C, 41·7; H, 3·0%).

(*b*) Benzimidazole (17·3 g.) was dissolved in ethanol (300 ml.) in which sodium (3·4 g.) had been dissolved. α-Chloro-*N*-methylacetamide [2] (16 g.) in ethanol (100 ml.) was slowly added, and the mixture refluxed for 4 hr. Sodium chloride was removed by filtration, and ethanol by evaporation. The residual oil solidified rapidly and was twice crystallised from ethyl methyl ketone to give 2-1′-*benzimidazolyl*-N-*methylacetamide* as needles (90%), m. p. 172° (Found: C, 63·7; H, 5·8. $C_{10}H_{11}ON_3$ requires C, 63·5; H, 5·9%). This compound (13·5 g.), lithium aluminium hydride (6 g.), and tetrahydrofuran (300 ml.) were refluxed for 6 hr. The excess of hydride was decomposed with tetrahydrofuran, and the combined extracts were dried ($NaSO_4$). On evaporation 2-1′-benzimidazolyl-*N*-methylethylamine was obtained as a colourless oil (95%) which rapidly became brown in the air. The infrared spectra of the dipicrates of the two products were identical.

2-1′-*Benzimidazolyl*-NN-*dimethylethylamine.* Similarly prepared from α-chloro-*NN*-dimethylacetamide,[2] 2-1′-*benzimidazolyl*-NN-*dimethylacetamide* was twice recrystallised from ethyl methyl ketone as plates, m. p. 139° (Found: C, 65·7; H, 6·9. $C_{11}H_{13}ON_3$ requires C, 65·0; H, 6·4%). 2-1′-*Benzimidazolyl*-NN-*dimethylethylamine dipicrate* recrystallised (twice) from water, forming yellow needles (60%), decomp. *ca.* 212° (Found: C, 42·3; H, 3·5. $C_{11}H_{15}N_3,2C_6H_3O_7N_3$ requires C, 42·7; H, 3·2%).

[1] Mamalis, Petrow, and Sturgeon, *J.*, 1950, 1600.
[2] Jacobs and Heidelberger, *J. Biol. Chem.*, 1915, **21**, 147.

2-1′-*Benzimidazolyl*-NN-*diethylethylamine*. (*a*) Similarly prepared from α-chloro-*NN*-diethylacetamide,[2] **2-1′-*benzimidazolyl*-NN-*diethylacetamide*** was recrystallised four times from water, forming needles (50%), m. p. 124° (Found: C, 68·4; H, 7·0; N, 17·5. $C_{13}H_{17}ON_3$ requires C, 67·5; H, 7·0; N, 18·2%). **2-1′-*Benzimidazolyl*-NN-*diethylethylamine dipicrate*** was recrystallised twice from water, forming yellow needles (60%), m. p. 220° (decomp.) (Found: C, 44·5; H, 3·7. $C_{13}H_{19}N_3,2C_6H_3O_7N_3$ requires C, 44·4; H, 3·7%).

(*b*) *NN*-Diethyl-*N′*-*o*-nitrophenylethylenediamine (10 g.) was catalytically reduced in alcohol (100 ml.) over Raney nickel at 5 atm. for 1 hr. The crude oily *N*-(2-diethylaminoethyl)-*o*-phenylenediamine obtained (95%) was refluxed for 40 min. with 4N-hydrochloric acid (100 ml.) and 87% formic acid (20 ml.). The product, basified with concentrated aqueous ammonia, was extracted four times with chloroform. On evaporation 2-1′-benzimidazolyl-*NN*-diethylethylamine was obtained as a brown oil from which the dipicrate, recrystallised thrice from water, was obtained as yellow needles (45%), m. p. and mixed m. p. 220—221° (decomp.) (identical infrared spectra).

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QUEEN'S COLLEGE, DUNDEE,
UNIVERSITY OF ST. ANDREWS. [*Received, January 19th, 1959.*]

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465. *The Reaction between 4-Nitrosoacetamidodiphenyl and Toluene. A Correction.*

By D. I. DAVIES, D. H. HEY, C. W. REES, and F. C. SAUNDERS.

IN an earlier communication it was reported by France, Heilbron, and Hey [1] that a mixture of 2-, 3-, and 4-methyl-*p*-terphenyl was formed in the reaction between 4-nitrosoacetamidodiphenyl and toluene. The constitutions assigned to the 2- and the 4-methyl derivative were established by independent syntheses. The third compound was regarded as 3-methyl-*p*-terphenyl by elimination. A repetition of this experiment has confirmed that the three isomers are formed, but the compound previously described as 3-methyl-*p*-terphenyl was in fact 4-acetamidodiphenyl. The 3-methyl-*p*-terphenyl now isolated agrees in properties with the compound prepared by Gilman and Weipert [2] by the reaction of 4-diphenylyllithium with 3-methylcyclohexanone followed by dehydration and dehydrogenation.

An attempt to prepare 4-nitrosoacetamidodiphenyl by the method of France, Heilbron, and Hey,[3] using nitrosyl chloride prepared by Bachmann and Hoffman's method,[4] gave a product which melted sharply at 116—117° and was shown unexpectedly to be an approximately equimolar mixture of 4-acetamido-3-nitrodiphenyl and 4-acetamido-3-chlorodiphenyl. When this preparation was repeated with pure redistilled nitrosyl chloride, 4-nitrosoacetamidodiphenyl was obtained which on reaction with benzene gave *p*-terphenyl and 4-acetamidodiphenyl. The use of nitrosyl chloride prepared by Bachmann and Hoffman's method without redistillation gave nitrosoacetanilide in the normal manner from acetanilide.

Experimental.—Reaction of 4-nitrosoacetamidodiphenyl with toluene. 4-Nitrosoacetamidodiphenyl was prepared from 4-acetamidodiphenyl and nitrous fumes, as described by France, Heilbron, and Hey.[5] A solution of the nitroso-compound (10 g.) in toluene (500 g.) was set aside at room temperature for 48 hr. It darkened and nitrogen was evolved. The reaction was completed by heating the solution on a boiling-water bath for 4 hr. The excess of the solvent was removed by distillation and the dark residue was boiled under reflux for 12 hr. with concentrated hydrochloric acid (100 ml.) and ethanol (100 ml.). The ethanol was then removed by distillation and the residue was extracted with hot benzene (4 × 100 ml.). The benzene

[1] France, Heilbron, and Hey, *J.*, 1939, 1283.
[2] Gilman and Weipert, *J. Org. Chem.*, 1957, **22**, 446.
[3] France, Heilbron, and Hey, *J.*, 1940, 369.
[4] Organic Reactions, Vol. II, John Wiley & Sons, Inc., New York, 1944, p. 251.
[5] France, Heilbron, and Hey, *J.*, 1938, 1364.

solution was filtered from some 4-aminodiphenyl hydrochloride and washed successively with concentrated hydrochloric acid, water, aqueous sodium hydroxide, and water. After having been dried ($CaCl_2$) the benzene was removed by distillation and the residue was distilled at 0·1 mm. to give two fractions: (*a*) bath-temp. 100—200°, b. p. *ca.* 70°/0·1 mm., a white solid (0·86 g.), which after crystallisation from light petroleum (b. p. 60—80°) had m. p. 65°, with an infrared spectrum (Nujol mull) practically identical with that of diphenyl; (*b*) bath-temp. 200—300°, b. p. *ca.* 130—170°/0·1 mm., a yellowish-brown semi-solid material (3·2 g.). Material (*b*) was shown to be mainly a mixture of 2- and 4-methyl-*p*-terphenyl by comparison of its infrared spectrum in cyclohexane solution with those of authentic specimens of 2- and 4-methyl-*p*-terphenyl. The whole fraction was dissolved in hot ethanol (100 ml.) and fractionally crystallised to give materials: (i) m. p. 180—190° (0·05 g.); (ii) m. p. 170—185° (0·03 g.); (iii) m. p. 130—160° (0·10 g.). The mother-liquor was then heated to the b. p. and water was added so that the solute was just not precipitated from the solution. From the cooled solution the following fractions were collected: (iv) m. p. 70° (0·60 g.); (v) m. p. 80—82° (0·30 g.); (vi) m. p. 84—86° (0·22 g.); (vii) m. p. >350° (0·04 g.). There was a residue of non-crystallisable oil. Fractions (i), (ii), and (iii) were combined and recrystallised from ethanol (charcoal) to constant m. p. 207—208°, which was not depressed on admixture with authentic 4-methyl-*p*-terphenyl. The infrared spectra of the two specimens were identical over the 2—15 μ range. Fraction (iv) in ethanol (25 ml.) was cooled to −5°, a yellow crystalline solid (0·05 g.) then separating (m. p. 110—115°). Several recrystallisations from methanol (charcoal) raised the m. p. to 125—126° (Found: C, 93·4; H, 6·65. Calc. for $C_{19}H_{16}$: C, 93·4; H, 6·6%), which was not depressed on admixture with a specimen of 3-methyl-*p*-terphenyl kindly provided by Professor H. Gilman. The infrared spectrum was consistent with this structure. Fractions (v) and (vi) were combined and recrystallisation from ethanol (charcoal) gave plates, m. p. 88—89°, which was not depressed on admixture with an authentic specimen of 2-methyl-*p*-terphenyl.

The infrared spectra of the above three methyl-*p*-terphenyls in Nujol mulls were measured over the range 2—15 μ. The main bands were as follows: 2-methyl-*p*-terphenyl 845·2(m), 761·8(s), 756·0(s), 736·9(w), 727·2(w), and 701·8(m) cm.$^{-1}$; 3-methyl-*p*-terphenyl 838·0(m), 813·0(m), 787·4(m), 760·7(s), 721·9(m) and 691·1(m) cm.$^{-1}$; 4-methyl-*p*-terphenyl 856·0(w), 817·8(s), 766·5(s), 730·9(m), 696·9(m) cm.$^{-1}$.

Reactions of 4-acetamidodiphenyl with nitrosyl chloride. When 4-acetamidodiphenyl was treated with nitrosyl chloride in glacial acetic acid–acetic anhydride in the presence of potassium acetate and phosphoric oxide, as described by France, Heilbron, and Hey,[3] a product was obtained which crystallised from light petroleum (b. p. 100—120°) in yellow needles, m. p. 116—117° (Found: C, 67·0, 66·5; H, 4·8, 5·0; N, 9·7, 9·5; Cl, 6·3, 5·7%). The nitrosyl chloride was prepared as described by Bachmann and Hoffman.[4] Fractional crystallisation of 1·0 g. from ethanol gave 4-acetamido-3-nitrodiphenyl in yellow needles, m. p. 134° (0·58 g.), while the mother-liquors gave 4-acetamido-3-chlorodiphenyl (0·19 g.), which separated from light petroleum (b. p. 80—100°) in needles, m. p. 147°. Separation was also effected by chromatography on alumina from benzene solution (0·5 g. gave 0·27 g. of 4-acetamido-3-nitrodiphenyl and 0·20 g. of 4-acetamido-3-chlorodiphenyl). 4-Acetamido-3-nitrodiphenyl was identified by hydrolysis to 4-amino-3-nitrodiphenyl, m. p. 171°, and subsequent benzoylation to give 4-benzamido-3-nitrodiphenyl, m. p. 150°, and reduction to 3,4-diaminodiphenyl, m. p. 100°. 4-Acetamido-3-chlorodiphenyl was identified by hydrolysis to 4-amino-3-chlorodiphenyl, m. p. 67°, and nitration to give 4-acetamido-3-chloro-4′-nitrodiphenyl, m. p. 220°. A mixture of 4-acetamido-3-nitrodiphenyl (55%) and 4-acetamido-3-chlorodiphenyl (45%) melts at 117—119° and requires C, 66·8; H, 4·8; N, 8·6; Cl, 6·4%.

Reaction of 4-acetamidodiphenyl with redistilled nitrosyl chloride, by the general procedure of France, Heilbron, and Hey,[3] gave 4-nitrosoacetamidodiphenyl as a yellow solid, m. p. 85° (decomp.). The nitroso-compound (2 g.), kept in benzene (100 ml.) for 46 hr., gave *p*-terphenyl (0·79 g.; m. p. and mixed m. p. 212°) and 4-acetamidodiphenyl (0·36 g.; m. p. and mixed m. p. 173°).

The authors are indebted to Professor H. Gilman for having drawn their attention to the earlier erroneous statements concerning 3-methyl-*p*-terphenyl, and for his assistance in clearing up the discrepancy.

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